

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 39/00, 39/38, 39/12, C12P 21/04, C12N 7/00, 7/01, 7/02, 7/04, 7/06, 7/08, 15/00, 15/09, 15/63, 15/70, 15/74</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/09646 (43) International Publication Date: 12 March 1998 (12.03.98)</p>
<p>(21) International Application Number: PCT/US97/12955 (22) International Filing Date: 31 July 1997 (31.07.97) (30) Priority Data: 08/708,541 5 September 1996 (05.09.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/708,541 (CIP) Filed on 5 September 1996 (05.09.96) (71) Applicant (for all designated States except US): UNIVER- SITY OF MARYLAND - BIOTECHNOLOGY INSTI- TUTE [US/US]; Suite 500, 4321 Hartwick Road, College Park, MD 20740 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): VAKHARIA, Vikram, N. [US/US]; 11332 Booth Bay Way, Bowie, MD 20720 (US). MUNDT, Egbert [DE/DE]; Ring Strasse 12, D-17498 Rieuserorf (DE).</p>		<p>(74) Agents: KITTS, Monica, Chin et al.; Nikaido, Marmelstein, Murray & Oram LLP, Suite 330, Metropolitan Square - "G" Street Lobby, 655 15th Street N.W., Washington, DC 20005-5701 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
<p>(54) Title: A METHOD FOR GENERATING BIRNAVIRUS FROM SYNTHETIC RNA TRANSCRIPTS (57) Abstract A system for the generation of live Birnavirus such as infectious bursal disease virus (IBDV), a segmented double-stranded (ds)RNA virus of the <i>Birnaviridae</i> family, using synthetic transcripts derived from cloned DNA has been developed. Independent full-length cDNA clones were constructed which contained the entire coding and non-coding regions of RNA segments A and B of IBDV, respectively. Synthetic RNAs of both segments were produced by <i>in vitro</i> transcription of linearized plasmids with T7 RNA polymerase. Transfection of Vero cells with combined plus-sense transcripts of both segments generated infectious virus as early as 36 hours post-transfection. The development of a reverse genetics system for dsRNA viruses will greatly facilitate studies of the regulation of viral gene expression pathogenesis, and design of a new generation of live and inactivated vaccines.</p>		

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A METHOD FOR GENERATING BIRNAVIRUS FROM SYNTHETIC RNA TRANSCRIPTS

Background of the Invention

Infectious bursal disease virus (IBDV), a member of the *Bimaviridae* family, is the causative agent of a highly immunosuppressive disease in young chickens (Kibenge, F.S.B., et al., *J. Gen. Virol.*, 69, 1757-1775 (1988)). Infectious bursal disease (IBD) or Gumboro disease is characterized by the destruction of lymphoid follicles in the bursa of Fabricius. In a fully susceptible chicken flock of 3-6 weeks of age the clinical disease causes severe immunosuppression, and is responsible for losses due to impaired growth, decreased feed efficiency, and death. Susceptible chickens less than 3 weeks old do not exhibit outward clinical signs of the disease but have a marked infection characterized by gross lesions of the bursa.

The virus associated with the symptoms of the disease is called infectious bursal disease virus (IBDV). IBDV is a pathogen of major economic importance to the nation and world's poultry industries. It causes severe immunodeficiency in young chickens by destruction of precursors of antibody-production B cells in the bursa of Fabricius. Immunosuppression causes increased susceptibility to other diseases, and interferes with effective vaccination against Newcastle disease, Marek's disease and infectious bronchitis disease viruses.

There are two known serotypes of IBDV. Serotype I viruses are pathogenic to chickens whereas serotype II viruses infect chickens and turkeys. The infection of turkeys is presently of unknown clinical significance.

IBDV belongs to a group of viruses called *Bimaviridae* which includes other bisegmented RNA viruses such as infectious pancreatic necrosis virus (fish), tellina virus and oyster virus (bivalve mollusks) and drosophila X virus (fruit fly). These viruses all contain high molecular weight (MW) double-stranded RNA genomes.

The capsid of the IBDV virion consists of several structural proteins. As many as nine structural proteins have been reported but there is evidence that some of these may have a precursor-product relationship (Kibenge,

F.S.B., et al., *J. Gen. Virol.*, 69, 1757-1775 (1988)). The designation and molecular weights of the viral proteins (VP) are as shown below.

5	Viral Protein	Molecular Weight
	VP1	90 kDa
	VP2	41 kDa
	VP3	32 kDa
	VP4	28 kDa
10	VP5	17 kDa

Two segments of double-stranded RNA were identified in the genome of IBDV. The IBDV genome consists of two segments of double-stranded (ds)RNA that vary between 2827 (segment B) to 3261 (segment A) nucleotide base pairs (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). The larger segment A encodes a polyprotein which is cleaved by autoproteolysis to form mature viral proteins VP2, VP3 and VP4 (Hudson, P.J. et al., *Nucleic Acids Res.*, 14, 5001-5012 (1986)). VP2 and VP3 are the major structural proteins of the virion. VP2 is the major host-protective immunogen of IBDV, and contains the antigenic regions responsible for the induction of neutralizing antibodies (Azad, et al., *Virology*, 161, 145-152 (1987)). A second open reading frame (ORF), preceding and partially overlapping the polyprotein gene, encodes a protein (VP5) of unknown function that is present in IBDV-infected cells (Mundt, E., et al., *J. Gen. Virol.*, 76, 437-443, (1995)). The smaller segment B encodes VP1, a 90-kDa multifunctional protein with polymerase and capping enzyme activities (Spies, U., et al., *Virus Res.*, 8, 127-140 (1987); Spies, U., et al., *J. Gen. Virol.*, 71, 977-981 (1990)).

It has been demonstrated that the VP2 protein is the major host protective immunogen of IBDV, and that it contains the antigenic region responsible for the induction of neutralizing antibodies. The region containing the neutralization site has been shown to be highly conformation-dependent. The VP3 protein has been considered to be a group-specific antigen because

it is recognized by monoclonal antibodies directed against it from strains of both serotype I and II viruses. The VP4 protein appears to be a virus-coded protease that is involved in the processing of a precursor polyprotein of the VP2, VP3 and VP4 proteins.

5 Although the nucleotide sequences for genome segments A and B of various IBDV strains have been published, it was only recently that the complete 5'- and 3'-noncoding sequences of both segments were determined. The 5'-noncoding region of IBDV segments A and B contain a consensus sequence of 32 nucleotides, whereas the 3'-noncoding terminal sequences
10 of both segments are unrelated, but conserved among IBDV strains of the same serotype (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). These termini might contain sequences important in packaging and in the regulation of IBDV gene expression, as demonstrated for other dsRNA containing viruses such as mammalian and plant reoviruses, and rotaviruses (Anzola, et al., *Proc. Natl. Acad. Sci. USA*, 84, 8301-8305 (1987); Zou, S., et al., *Virology*, 186, 377-388 (1992); Gorziglia, M.I., et al., *Proc. Natl. Acad. Sci. USA*, 89, 5784-5788 (1992)).

 In recent years, a number of infectious animal RNA viruses have been generated from cloned cDNA using transcripts produced by DNA-dependent
20 RNA polymerase (Boyer, J.C., et al., *Virology*, 198, 415-426 (1994)). For example poliovirus, a plus-stranded RNA virus; influenza virus, a segmented negative-stranded RNA virus; rabies virus, a non-segmented negative-stranded RNA virus; all were recovered from cloned cDNAs of their respective genomes (van der Werf, S., et al., *Proc. Natl. Acad. Sci. USA*, 83, 2330-2334 (1986); Enami, M., et al., *Proc. Natl. Acad. Sci. USA*, 87, 3802-3805 (1990); Schnell, M.J., et al., *EMBO J.*, 13, 4195-4205 (1994)). For reovirus, it was shown that transfection of cells with a combination of SSRNA, dsRNA and *in vitro* translated reovirus products generated infectious reovirus when complemented with a helper virus from a different serotype (Roner, M.R., et al., *Virology*, 179, 845-852 (1990)). However, to date, there has been no
30 report of a recovered infectious virus of segmented dsRNA genome from synthetic RNAs only.

Summary of the Invention

This invention relates to the infectious bursal disease virus (IBDV) that is associated with Gumboro disease of young chickens. More particularly, this invention relates to a system for the generation of infectious bursal disease virus (IBDV) using synthetic transcripts derived from cloned cDNA. The present invention will facilitate studies of the regulation of viral gene expression, pathogenesis and design of a new generation of live and inactivated vaccines.

Detailed Description of the Invention

In an effort to develop a reverse genetics system for IBDV, three independent full-length cDNA clones which contain segment A of serotype I strain D78 or serotype II strain 23/82 and segment B of the serotype I strain P2, respectively, were constructed. Synthetic RNAs of segments A and B were produced by *in vitro* transcription reaction on linearized plasmids with T7 RNA polymerase. Transcripts of these segments, either untreated or treated with DNase or RNase, were evaluated for the generation of infectious virus by transfection of Vero cells.

The present inventors have demonstrated that synthetic transcripts derived from cloned DNA corresponding to the entire genome of a segmented dsRNA animal virus can give rise to a replicating virus. The recovery of infectious virus after transfecting cells with synthetic plus-sense RNAs derived from cloned cDNA of a virus with a dsRNA genome (IBDV) completes the quest of generating reverse infectious systems for RNA viruses. A number of investigators have generated infectious animal RNA viruses from cloned cDNA (Boyer, J.C., et al., *Virology*, 198, 415-426 (1994)). Van der Werf et al. were first to generate poliovirus, a plus-stranded RNA virus, using synthetic RNA produced by T7 RNA polymerase on cloned cDNA template (van der Werf, S., et al., *Proc. Natl. Acad. Sci. USA*, 83, 2330-2334 (1986)). later, Enami et al. rescued influenza virus, a segmented negative-stranded RNA virus (Enami, M., et al., *Proc. Natl. Acad. Sci. USA*, 87, 3802-3805 (1990)); and Schnell et al. generated rabies virus, a non-segmented negative-stranded RNA virus, from cloned cDNAs of their respective genomes (Schnell, M.J., et

al., *EMBO J.*, 13, 4195-4205 (1994)). Roner et al. developed an infectious system for a segmented dsRNA reovirus by transfecting cells with a combination of synthetic ssRNA, dsRNA, *in vitro* translated reovirus products, and complemented with a helper virus of different serotype (Roner, M.R., et al., *Virology*, 179, 845-852 (1990)). The resulting virus was discriminated from the helper virus by plaque assay. However, in this system the use of a helper virus was necessary. In contrast, the presently described reverse genetics system of IBDV does not require a helper virus or other viral proteins. Transfection of cells with plus-sense RNAs of both segments was sufficient to generate infectious virus (IBDV). The fate of the additional one or four nucleotides, respectively, transcribed at the 3'-end of segment A was not determined. However, this did not prevent the replication of the viral dsRNA. Similar effects were observed for plus-stranded RNA viruses by different investigators (Boyer, J.C., et al., *Virology*, 198, 415-426 (1994)).

Transfection of plus-sense RNAs of both segments into the same cell was necessary for the successful recovery of IBDV. Transfected RNAs of both segments had to be translated by the cellular translation machinery. The polyprotein of segment A was presumably processed into VP2, VP3 and VP4 proteins which form the viral capsid. The translated protein VP1 of segment B probably acted as a RNA-dependent RNA polymerase and transcribed minus-strands from synthetic plus-strands of both segments, and the reaction products formed dsRNA. Recently, Dobos reported that *in vitro* transcription by the virion RNA-dependent RNA polymerase of infectious pancreatic necrosis virus (IPNV), a prototype virus of the *Bimaviridae* family, is primed by VP1 and then proceeds via an asymmetric, semiconservative, strand-displacement mechanism to synthesize only plus strands during replication of the viral genome (Dobos, P., *Virology*, 208, 10-25 (1995)). The present system shows that synthesis of minus-strands proceeds on the plus-strands. Whether the resulting transcribed minus-strand RNA serves as a template for the transcription of plus-strands or not remains the subject of further investigation.

To prove that the infectious IBDV contained in the supernatants of transfected cells was indeed derived from the synthetic transcripts, an artificial chimera was generated containing segment A of a serotype II strain and segment B of a serotype I strain. Sequence analysis verified this genome combination. The results also indicate that the terminal sequence motifs described by Mundt and Müller are probably responsible for replication, sorting and packaging of the viral genome (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). Presence of serotype-specific terminal sequences obviously does not prevent proper replication of serotype II A segment by the action of the RNA-dependent RNA polymerase VP1 of the serotype I segment B. The ability to create recombinant viruses will greatly help in analyzing the precise function of serotype-specific and serotype-common terminal sequences.

The recovery of infectious IBDV demonstrates that only the plus-strand RNAs of both segments are sufficient to initiate replication of dsRNA. Thus, the results are in agreement with the general features of reovirus and rotavirus replication where the plus-strand RNAs serve as a template for the synthesis of progeny minus-strands to yield dsRNA (Schonberg, M., et al., *Proc. Natl. Acad. Sci. Patton, J.T., Virus Res.*, 6, 217-233 (1986); Chen, D., et al., *J. Virol.*, 68, 7030-7039 (1994)). However, the semiconservative, strand displacement mechanisms proposed by Spies et al. and Dobos could not be excluded (Spies, U., et al., *Virus Res.*, 8, 127-140 (1987); Dobos, P., *Virology*, 208, 10-25 (1995)). The development of a reverse genetics system for IBDV will greatly facilitate future studies of gene expression, pathogenesis, and help in the design of new generations of live and inactivated IBDV vaccines.

As used in the present application, the term "synthetic" as applied to nucleic acids indicates that it is a man made nucleic acid in contrast to a naturally occurring nucleic acid. The term implies no limitation as to the method of manufacture, which can be chemical or biological as long as the method of manufacture involves the intervention of man.

The term "cDNA" is intended to encompass any cDNA containing segments A and B and the 5' and 3' noncoding regions of segments A and B.

The term "infectious" as applied to viruses indicates that the virus has the ability to reproduce. The virus can be pathogenic or nonpathogenic and still be infectious.

5 The present invention provides a system for the generation of infectious bursal disease virus using synthetic RNA transcripts. This system can be used to study the regulation of viral gene expression, pathogenesis, and for the design of a new generation of live and inactivated IBDV vaccines.

10 The present invention provides a recombinant vector containing at least one copy of the cDNA according to the present invention. The recombinant vector may also comprise other necessary sequences such as expression control sequences, markers, amplifying genes, signal sequences, promoters, and the like, as is known in the art. Useful vectors for this purpose are plasmids, and viruses such as baculoviruses, herpes virus (HVT) and pox viruses, e.g., fowl pox virus, and the like.

15 Also provided herein is a host cell transformed with the recombinant vector of the present invention or a host cell transfected with the synthetic RNA of the present invention. The host cell may be a eukaryotic or a prokaryotic host cell. Suitable examples are *E. coli*, insect cell lines such as Sf-9, chicken embryo fibroblast (CEF) cells, chicken embryo kidney (CEK) cells, African green monkey Vero cells and the like.

20 Also part of this invention is an IBDV poultry vaccine comprising a poultry protecting amount of a recombinantly produced virus or portion of a virus, wherein the virus is inactivated or modified such that it is no longer virulent.

25 The virus can be inactivated by chemical or physical means. Chemical inactivation can be achieved by treating the virus with, for example, enzymes, formaldehyde, β -propiolactone, ethylene-imine or a derivative thereof, an organic solvent (e.g. halogenated hydrocarbon) and or a detergent. If necessary, the inactivating substance can be neutralized after the virus has been inactivated. Physical inactivation can be carried out by subjecting the viruses to radiation such as UV light, X-radiation, or γ -radiation.

30

The virus can be attenuated by known methods including serial passage, deleting sequences of nucleic acids and site directed mutagenesis either before or after production of the infectious virus to produce a virus which retains sufficient antigenicity but which has reduced virulence.

5 Physiologically acceptable carriers for vaccination of poultry are known in the art and need not be further described herein. In addition to being physiologically acceptable to the poultry the carrier must not interfere with the immunological response elicited by the vaccine and/or with the expression of its polypeptide product.

10 Other additives, such as adjuvants and stabilizers, among others, may also be contained in the vaccine in amounts known in the art. Preferably, adjuvants such as aluminum hydroxide, aluminum phosphate, plant and animal oils, and the like, are administered with the vaccine in amounts sufficient to enhance the immune response to the IBDV. The amount of
15 adjuvant added to the vaccine will vary depending on the nature of the adjuvant, generally ranging from about 0.1 to about 100 times the weight of the IBDV, preferably from about 1 to about 10 times the weight of the IBDV.

 The vaccine of the present invention may also contain various stabilizers. Any suitable stabilizer can be used including carbohydrates such
20 as sorbitol, mannitol, starch, sucrose, dextrin, or glucose; proteins such as albumin or casein; and buffers such as alkaline metal phosphate and the like. A stabilizer is particularly advantageous when a dry vaccine preparation is prepared by lyophilization.

 The vaccine can be administered by any suitable known method of
25 inoculating poultry including nasally, ophthalmically, by injection, in drinking water, in the feed, by exposure, and the like. Preferably, the vaccine is administered by mass administration techniques such as by placing the vaccine in drinking water or by spraying the animals' environment. When administered by injection, the vaccines are preferably administered
30 parenterally. Parenteral administration as used herein means administration by intravenous, subcutaneous, intramuscular, or intraperitoneal injection.

The vaccine of the present invention is administered to poultry to prevent IBD anytime before or after hatching. Preferably, the vaccine is administered prior to the time of birth and after the animal is about 6 weeks of age. Poultry is defined to include but not be limited to chickens, roosters, hens, broilers, roasters, breeders, layers, turkeys and ducks.

The vaccine may be provided in a sterile container in unit form or in other amounts. It is preferably stored frozen, below -20°C , and more preferably below -70°C . It is thawed prior to use, and may be refrozen immediately thereafter. For administration to poultry the recombinantly produced virus may be suspended in a carrier in an amount of about 10^4 to 10^7 pfu/ml, and more preferably about 10^5 to 10^6 pfu/ml in a carrier such as a saline solution. The inactivated vaccine may contain the antigenic equivalent of 10^4 to 10^7 pfu/ml suspended in a carrier. Other carriers may also be utilized as is known in the art. Examples of pharmaceutically acceptable carriers are diluents and inert pharmaceutical carriers known in the art. Preferably, the carrier or diluent is one compatible with the administration of the vaccine by mass administration techniques. However, the carrier or diluent may also be compatible with other administration methods such as injection, eye drops, nose drops, and the like.

The invention also can be used to produce combination vaccines with the IBDV material. The IBDV material can be combined with antigen material of Newcastle Disease Virus Infectious Bronchitis virus, Reo virus, Adeno virus and/or the Marek virus.

The foregoing embodiments of the present invention are further described in the following Examples. However, the present invention is not limited by the Examples, and variations will be apparent to those skilled in the art without departing from the scope of the present invention.

Brief Description of the Drawings

Figure 1 is a schematic diagram of cDNA constructs used for synthesis of plus-sense ssRNAs of IBDV with T7 RNA polymerase. Construct pUC19FLAD78 contains the cDNA of segment A of IBDV strain D78 and the recombinant plasmid pUC18FLA23 contains the full-length cDNA of segment

A of IBDV strain 23/82. Segment A of IBDV encodes the polyprotein (VP2-VP4-VP3), and the recently identified VP5 protein. Plasmid pUC18FLBP2 contains the cDNA of segment B of strain P2 which encodes the RNA-dependent RNA polymerase (VP1). Virus specific sequences are underlined and the T7 promoter sequences are italicized. Restriction sites are shown in boldface and identified. The cleavage sites of the linearized plasmids are shown by vertical arrows and the transcription directions are marked by horizontal arrows.

Figure 2 shows an agarose gel analysis of the transcription reaction products that were used for transfection of Vero cells. Synthetic RNAs transcribed *in vitro* using T7 RNA polymerase and linearized plasmids pUC19FLAD78 (lanes 2, 4 and 6) containing the cDNA of segment A of IBDV strain D78, and pUC18FLBP2 (lanes 1, 3 and 5) containing the cDNA of segment B of strain P2, respectively. After transcription, the reaction mixtures were either treated with DNase (lanes 1 and 2), RNase (lanes 3 and 4) or left untreated (lanes 5 and 6). Two μ l of the reaction products were analyzed on 1% agarose gel. Lambda DNA, digested with *Hind* III/*Eco*R I, was used as markers (lane M).

Figure 3 shows a comparison of nucleotide sequences of cloned RT-PCR fragments from segments A and B of the chimeric IBDV strain 23A/P2B (bold-typed) with known sequences of segments A and B of serotype II strain 23/82 and serotype I strain P2, respectively. Nucleotide identities are marked by a colon.

Figure 4 shows the DNA sequence of pUC18FLA23.

Figure 5 shows the DNA sequence of pUC19FLAD78.

Figure 6 shows the DNA sequence of pUC18FLBP2.

EXAMPLES

Viruses and Cells. Two serotype I strains of IBDV, the attenuated P2 strain from Germany and the vaccine strain D78 (Intervet International), and one serotype II strain, the apathogenic 23/82 strain, were propagated in chicken embryo cells (CEC) and purified (Mundt, E. et al., *Virology*, 209, 10-18 (1995); Vakharia, V.N., et al., *Virus Res.*, 31, 265-273 (1994)). Vero cells

were grown in M199 medium supplemented with 5% fetal calf serum (FCS) and used for transfection experiments. Further propagation of the recovered virus and immunofluorescence studies were carried out in Vero cells (Mundt, E., et al., *J. Gen. Virol.*, 76, 437-443, (1995)). For plaque assay, monolayers of secondary CEC were prepared and used (Müller, H., et al., *Virus Res.*, 4, 297-309 (1986)).

Construction of Full-Length cDNA Clones of IBDV genome. Full-length cDNA clones of IBDV segments A and B were independently prepared. The cDNA clones containing the entire coding region of the RNA segment A of strain D78 were prepared using standard cloning procedures and methods (Vakharia, V.N., et al., *Virus Res.*, 31, 265-273 (1994)). By comparing the D78 terminal sequences with recently published terminal sequences of other IBDV strains (Mundt, E. et al., *Virology*, 209, 10-18 (1995)), it was observed that D78 cDNA clones lacked the conserved first 17 and last 10 nucleotides at the 5'- and 3'-ends, respectively. Therefore, to construct a full-length cDNA clone of segment A, two primer pairs (A5'-D78, A5-IPD78 and A3'-IPD78) were synthesized and used for PCR amplification (Table 1). The DNA segments were amplified according to the protocol of the supplier (New England Biolabs) using "Deep Vent Polymerase" (high fidelity thermophilic DNA polymerase). Amplified fragments were cloned into the *EcoR* I site of a pCRII vector (Invitrogen Corp.) to obtain plasmids pCRD78A5' and pCRD78A3', respectively. Each plasmid was digested with *EcoR* I and *Sal* I and the resultant fragments were ligated into *EcoR* I digested pUC19 to obtain plasmid pUC19FLAD78 (SEQ ID NOS:27 AND 29) which now contains a full-length cDNA copy of segment A encoding all the structural proteins (VP2, VP4 and VP3, SEQ ID NO:30) as well as the non-structural VP5 protein (SEQ ID NO:28) (Fig. 1).

Two primer pairs (A5'-23, A5IP23 and A3'-23, A3-IP23; see Table 1) were used for reverse transcription (RT) of viral genomic dsRNA of strain 23/82 using "SuperScript RT II" (RNA directed DNA polymerase with reduced RNase H activity, GIBCO/BRL). The RT reaction products were purified by phenol/chloroform extraction and ethanol precipitation. To obtain two cDNA

fragments bounded by primer pairs A5'-23, A5-IP23 and A3'-23, A3-IP23, respectively, RT reaction products were amplified by PCR using "Deep Vent polymerase". Both RT and PCR were carried out according to the supplier's protocol. Resulting PCR fragments were blunt-end ligated into *Sma* I cleaved pUC18 vector to obtain pUC23A5' and pUC23A3'. The 3'-end of segment A contained in plasmid pUC23A3' was ligated into the *Hind* III-*Bst* B I cleaved plasmid pUC23A5' to establish the full-length cDNA of segment A of strain 23/82. The resulting plasmid was termed pUC18FLA23 (SEQ ID NOS: 31 AND 33)(Fig. 1) and encodes structural proteins VP2, VP3 and VP4 (SEQ ID NO: 32) and non-structural protein VP5 (SEQ ID NO: 34)

To obtain cDNA clones of segment B of P2 strain, two primer pairs (B5'-P2, B5-IPP2 and B3'-P2, B3-IPP2) were designed according to the published sequences and used for RT-PCR amplification (see Table 1). Using genomic dsRNA as template, cDNA fragments were synthesized and amplified according to the supplier's protocol (Perkin-Elmer Cetus). Amplified fragments were blunt-end ligated into *Sma* I cleaved pBS vector (Stratagene) to obtain clones pBSP2B5' and pBSP2B3'. To construct a full-length clone of segment B, the 5'-end fragment of plasmid pBSP2B5' was first subcloned between *Eco*R I and *Pst* I sites of pUC18 vector to obtain pUCP2B5'. Then the 3'-end fragment of plasmid pBSP2B3' was inserted between the unique *Bgl* II and *Pst* I sites of plasmid pUCP2B5' to obtain a full-length plasmid pUC18FLBP2 (SEQ ID NO:25) which encodes the VP1 protein (SEQ ID NO: 26) (Fig. 1). Plasmids pUC18FLBP2, pUC18FLA23 and pUC19FLAD78 were completely sequenced by using the "Sequenase" DNA sequencing system (U.S. Biochem.), and the sequence data were analyzed using either "DNASIS" (Pharmacia) or "PC/Gene" (Intelligenetics) software. The integrity of the full-length constructs was tested by *in vitro* transcription and translation coupled reticulocyte lysate system using T7 RNA polymerase (Promega).

Transcription and Transfection of Synthetic RNAs. Plasmids pUC19FLAD78, pUC18FLA23 and pUC18FLBP2 were digested with *Bsr* G I, *Nsi* I and *Pst* I enzymes (see Fig. 1), respectively, and used as templates for *in vitro* transcription with T7 RNA polymerase (Promega). Briefly, restriction

enzyme cleavage assays were adjusted to 0.5% SDS and incubated with proteinase K (0.5 mg/ml) for 1 hour at 37°C. The linearized DNA templates (~3 µg) were recovered after ethanol precipitation, and were added separately to a transcription reaction mixture (50 µl) containing 40 mM Tris-HCl (pH 7.9), 10 mM NaCl, 6 mM MgCl₂, 2 mM spermidine, 0.5 mM ATP, CTP and UTP each, 0.1 mM GTP, 0.25 mM cap analog [m⁷G(5') PPP(5') G], 120 units of "RNasin" (ribonuclease inhibitor), 150 units T7 RNA polymerase (Promega), and incubated at 37°C for 1 hour. Synthetic RNA transcripts were purified by phenol/chloroform extraction and ethanol precipitation. As controls, the transcription products were treated with either DNase or RNase (Promega) before the purification step.

Vero cells were grown to 80% confluence in 60 mm dishes and washed once with phosphate-buffered saline (PBS). Three ml of "OPTI-MEM I" (reduced serum medium containing HEPES buffer, sodium bicarbonate, hypoxanthine, thymidine, sodium pyruvate, L-glutamine, trace elements, growth factors and phenol red; from GIBCO/BRL) were added to the monolayers, and the cells were incubated at 37°C for 1 hour in a CO₂ incubator. Simultaneously, 0.15 ml of "OPTI-MEM I" was incubated with 1.25 µg of "Lipofectin" reagent (N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride and dioleoylphosphatidylethanolamine, GIBCO/BRL) for 45 min. in a polystyrene tube at room temperature. Synthetic RNA transcripts of both segments, resuspended in 0.15 ml of diethyl pyrocarbonate-treated water, were added to the OPTI-MEM-Lipofectin-mixture, mixed gently, and incubated on ice for 5 min. After removing the "OPTI-MEM" from the monolayers in 60 mm dishes and replacing with fresh 1.5 ml of "OPTI-MEM", the nucleic acid containing mixture was added dropwise to the Vero cells and swirled gently. After 2 hours of incubation at 37°C, the mixture was replaced with M199 medium [CaCl₂ (anhydrous), Fe(NO₃)₃ 9H₂O, KCl, MgSO₄ (anhydrous), NaCl, NaH₂PO₄·H₂O, NaHCO₃, L-Alanine, L-Arginine HCl, L-Aspartic acid, L-Cysteine HCl H₂O, L-Cysteine 2HCl, L-Glutamic acid, L-Glutamine, Glycine, L-Histidine HCl H₂O, L-Hydroxyproline, L-Isoleucine, L-Leucine, L-Lysine HCl, L-Methionine, L-Phenylalanine, L-

Proline, L-Serine, L-Threonine, L-Tryptophan, L-Tyrosine 2Na 2H₂O, L-Valine, Alpha tocopherol PO₄ Na₂, Ascorbic Acid, Biotin, Calciferol, D-Calcium pantothenate, Choline chloride, Folic acid, I-Inositol, Menandione NaHSO₃ 3H₂O, Niacin, Nicotinamide, Para-aminobenzoic acid, Pyridoxine HCl, 5 Riboflavin, Thiamine HCl, Vitamin A Acetate, Adenine SO₄, Adenylic Acid, ATP, Na₂, Cholesterol, 2-Deoxy-D-Ribose, D-Glucose, Glutathione, Guanine HCl, Hypoxanthine Na, Phenol Red Na, Ribose, Sodium Acetate (anhydrous), Thymine, Tween 80, Uracil, and Xanthine Na; from Mediatech, Inc.] containing 5% FCS (without rinsing cells) and the cells were further incubated at 37°C 10 for desired time intervals.

Identification of Generated IBDV. CEC were infected with filtered (0.2 µm) supernatant from Vero cells transfected with transcripts of pUC18FLA23 and pUC18FLP2B. 16 hours post-infection, the whole cell nucleic acids were isolated (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). 15 Primers were designed according to the published sequences and RT-PCR fragments were amplified, cloned and sequenced (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). Sequence data were analyzed by using "DNASIS" software.

20 **Immunofluorescence.** Vero cells, grown on cover slips to 80% confluence, were infected with the supernatants derived from transfected Vero cells (after freeze-thawing) and incubated at 37°C for two days. The cells were then washed, fixed with acetone and treated with polyclonal rabbit anti-IBDV serum. After washing, the cells were treated with fluorescein 25 labeled goat-anti-rabbit antibody (Kirkegaard & Perry Lab.) and examined by fluorescence microscope.

Plaque Assay. Monolayers of secondary CEC, grown in 60 mm dishes, were inoculated with the supernatants derived from transfected Vero cells. After 1 hour of infection, the cells were washed once with PBS and 30 overlaid with 0.8% Agar noble (Difco) containing 10% tryptose phosphate broth, 2% FCS, 0.112% NaHCO₃, 10³ units penicillin, 10³ µg/ml streptomycin, 0.25 µg/ml fungizone, 0.005% neutral red, 0.0015% phenol red. The cells

were incubated at 37°C for 2 to 3 days until plaques could be observed and counted (Müller, H., et al., *Virus Res.*, 4, 297-309 (1986)).

Construction of Full-Length cDNA clones of IBDV Genome. To develop a reverse genetics system for the dsRNA virus IBDV, two independent cDNA clones were constructed that contain segment A of strain D78 and segment B of strain P2 (Fig. 1). Each plasmid encoded either the precursor of structural proteins (VP2, VP4, VP3) and VP5 or only VP1 protein (RNA-dependent RNA polymerase). Plasmid pUC18FLBP2 upon digestion with *Pst* I and transcription *in vitro* by T7 RNA polymerase, would yield RNA containing the correct 5'- and 3'-ends. Whereas, upon digestion with *Bsr*G I and transcription, plasmid pUC19FLAD78 would yield RNA containing the correct 5'-end but with additional four nucleotides at the 3'end. Coupled transcription and translation of the above plasmids in a rabbit reticulocyte system yielded protein products that were correctly processed and comigrated with the marker IBDV proteins after fractionating on SDS-polyacrylamide gel and autoradiography (data not shown).

Transcription, Transfection and Generation of Infectious Virus. Plus-sense transcripts of IBDV segment A and B were synthesized separately *in vitro* with T7 RNA polymerase using linearized full-length cDNA plasmids as templates (see Fig. 2). Although two species of RNA transcripts were observed for segment B on a neutral gel (lanes 1 and 5), fractionation of these samples on a denaturing gel yielded only one transcript-specific band (data not shown). In order to show that plus-sense RNA transcripts of both segments are needed for the generation of infectious virus, the transcription mixtures were incubated with different nucleases, as shown in Fig. 2. Synthetic RNAs recovered after treating the transcription products with DNase (lanes 1+2), RNase (lanes 3+4) or without treatment (lanes 5+6), were used for the transfection of Vero cells. As mock control, Lipofectin alone was used. Five days post-transfection, cytopathic effect (CPE) was only visible in Vero cells transfected with combined transcripts of untreated or DNase-treated transcription products, but not with RNase-treated transcription mixtures or

mock-transfected control. In addition, no CPE was detected when Vero cells were transfected with RNA of only segment A or B (data not shown). These results demonstrate that replication of IBDV ensued after transfection of Vero cells with plus-sense ssRNAs of both segments of IBDV. To verify that the agent causing the CPE in Vero cells was indeed IBDV, transfected Vero cells were freeze-thawed, and supernatants were clarified by centrifugation, and used to infect CEC or Vero cells. CEC infected with the supernatants derived from Vero transfected cells of untreated or DNase-treated transcription mixtures produced CPE in one day post-inoculation (Table 2). However, no CPE could be detected even after five days in CEC, with the supernatants from transfected Vero cells of RNase-treated transcription mixtures, untreated segment A or B transcription mixtures and mock-transfected Vero cells. Similarly, when Vero cells on cover slips were infected with the same supernatants as described above and examined by immunofluorescence staining after 2 days, only supernatants derived from transfected Vero cells of untreated or DNase-treated transcription mixtures gave positive immunofluorescence signal (Table 2).

Recovery of Transfectant Virus. To determine the time point for the recovery of infectious virus, Vero cells were transfected with combined RNA transcripts of segments A and B. At 4, 8, 16, 24, 36 and 48 hours post-transfection, the supernatants were examined for the presence of transfectant virus by infectivity and plaque assays, as shown in Table 3. Our results indicate that the virus could be recovered as early as 36 hours after transfection. Virus titer was 2.3×10^2 pfu/ml which appear to drop for samples obtained later than 48 hours after transfection.

Generation of a Chimeric Virus. To prove that plus-sense ssRNA of both segments of IBDV are sufficient for recovery of infectious virus, a chimeric IBDV was generated. Plasmid pUC18FLA23 containing a full-length sequence of segment A of serotype II strain was linearized by *Nsi* I digestion and ssRNA was synthesized *in vitro* using T7 RNA polymerase. The ssRNA transcript specifies the correct 5'-end but contains one additional residue at the 3'-end (Fig. 1). Vero cells were transfected with ssRNA of segment A of

serotype II strain 23/82 and ssRNA of segment B of serotype I strain P2. Five days after transfection when CPE was evident, the supernatant was clarified (after freeze-thawing) and used to infect CEC. After a second passage in CEC, genomic RNA of the virus was analyzed by RT-PCR and sequencing of the PCR products. Primers for segment A were designed to specifically amplify only segment A sequences derived from the serotype II strain. Primer for segment B bound to sequences of both serotypes. The amplified fragments were cloned and sequenced. The obtained segment A sequences showed a perfect match with known segment A sequences of serotype II strain 23/82, whereas segment B sequence exhibited complete homology to published segment B sequences of serotype I strain P2 (Fig. 3).

Table 1. Oligonucleotides Used for the Construction of Full Length cDNA Clones of IBDV Genomic Segments A and B.

Nucleotide Sequence	Orientation	Name	Nucleotide Number
<u>TAATACGACTCACTATAGGATACGATCGGICTGACCCCGGGGAGTCA</u>	(+)	A5'-D78	1-31
AGAGAAATTCATAACGACTCACTATAGGATACGATCGGICTGAC	(+)	A5'-23	1-48
TGTACAGGGGACCCCGGAACGGATCCAAT	(-)	A3'-D78	3237-3261
CGCGGAATTCATGCATAGGGGACCCCGGAACGGATC	(-)	A3'-23	3242-3261
<u>CGTCGACTACGGGATTCCTGG</u>	(-)	A5-IPD78	1711-1730
CAGAGGCAGTACTCCGCTCG	(-)	A5-IP23	1971-1990
<u>AGTCGACGGGATTCCTGCTT</u>	(+)	A3-IPD78	1723-1742
<u>GAAGGTGTGCGAGAGGAC</u>	(+)	A3-IP23	1883-1900
AGAGAAATTCATAACGACTCACTATAGGATACGATCGGICTGAC	(+)	B5'-P2	1-18
CGATCTGCTGCAGGGGCCCCCGCAGGCGAAGG	(-)	B3'-P2	2807-2827
<u>CTTGAGACTCTTGTCTCTACTCC</u>	(-)	B5-IPP2	1915-1938
<u>ATACAGCAAGATCTCGGG</u>	(+)	B3-IPP2	1839-1857

Composition and location of the oligonucleotide primers used for cloning. T7 promoter sequences are marked with italic types, the virus specific sequences are underlined, and the restriction sites marked in boldface. Orientation of the virus specific sequence of the primer is shown for sense (+) and antisense (-). The positions where the primers bind (nucleotide number) are according to the published sequences of P2 strain (2).

Table 2. Generation of Infections IBDV From Synthetic RNAs of Segment A and B.

Material Transfected	CPE	Immunofluorescence
ssRNA A+B, DNase-treated	+	+
ssRNA A+B, RNase-treated	-	-
ssRNA A+B, untreated	+	+
ssRNA A, untreated	-	-
ssRNA B, untreated	-	-
Lipofectin only	-	-

Vero cells were transfected with synthetic RNAs of segment A and B derived from transcription reactions that were either untreated or treated with DNase or RNase. After 5 days, the supernatants were collected, clarified by centrifugation, and analyzed for the presence of virus. The infectivity of the recovered virus was determined in CEC by the appearance of cytopathic effect (CPE) 1-2 days post-inoculation. The specificity of the recovered virus was determined by immunofluorescence staining of infected Vero cells with rabbit anti-IBDV serum.

Table 3. Recovery of Virus at Various Times Post-Transfection.

Time in hours post-transfection	CPE	Immunofluorescence	pfu/ml
4	-	-	0
8	-	-	0
16	-	-	0
24	-	-	0
36	+	+	2.3×10^2
48	+	+	6.0×10^1

Vero cells were transfected with synthetic RNAs of segment A and B as described. The infectivity and specificity of the recovered virus was detected by CPE in CEC and immunofluorescence staining in Vero cells, respectively. Monolayers of secondary CEC were used for plaque assay after inoculating the cells with the supernatants derived from transfected Vero cells. Approximate titer of the virus was calculated as plaque forming units per ml (pfu/ml).

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: A METHOD FOR GENERATING BIRNAVIRUS
FROM SYNTHETIC RNA TRANSCRIPTS

(iii) NUMBER OF SEQUENCES: 34

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(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US

(B) FILING DATE:

(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 46 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

22

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GAATTCGGCT TTAATACGAC TCACTATAGG ATACGATCGG TCTGAC

46

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

AATTGGATCC GTTCGCGGGT CCCCTGTACA AAGCCGAATT C

41

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CGGCGAATTC ATGCATAGGG GACCCGCGAA CGGATC

36

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GTCAGACCGA TCGTATCCTA TAGTGAGTCG TATTAGAATT CTCT

44

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TTGCATGCCT GCAGGGGGCC CCCGCAGGCG AAG

33

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 31 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCGTATCCTA TAGTGAGTCG TATTAGAATT C

31

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 120 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGAAGCCTGA GTGAGTTGAC TGA CTACAGC TACAACGGGC TGATGTCAGC CACTGCCAAC 60
ATCAACGACA AGATCGGGAA CGTTCTAGTT GGAGAAGGGG TGACTGTTCT CAGTCTACCG 120

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 120 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GGAAGCCTGA GTGAGTTGAC TGACTACAGC TACAACGGGC TGATGTCAGC CACTGCGAAC 60

ATCAACGACA AGATCGGGAA CGTTCTAGTT GGAGAAGGGG TGACTGTTCT CAGTCTACC 119

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 120 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGAAGCCTGA GTGAACTGAC AGATGTTAGC TACAATGGGT TGATGTCTGC AACAGCCAAC 60

ATCAACGACA AAATTGGGAA CGTCCTAGTA GGGGAAGGGG TCACCGTCCT CAGCTTACCC 120

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 120 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTTTCAATAG TCCACAGGCG CGAACGAAGA TCTCAGCAGC GTTCGGCATA AAGCCTACTG 60

CTGGACAAGA CGTGGAAGAA CTCTTGATCC CCAAAGTCTG GGTGCCACCT GAGGATCCGC 120

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 120 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TTTTCAACAG TCCACAGGCG CGAAGCACGA TCTCAGCAGC GTTCGGCATA AAGCCTACTG 60
CTGGACAAGA CGTGGAAGAA CTCTTGATCC CTAAAGTTTG GGTGCCACCT GAGGATCCGC 120

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 120 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

TTTTCAACAG TCCACAGGCG CGAAGCACGA TCTCAGCAGC GTTCGGCATA AAGCCTACTG 60
CTGGACAAGA CGTGGAAGAA CTCTTGATCC CTAAAGTTTG GGTGCCACCT GAGGATCCGC 120

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TAATACGACT CACTATAGGA TACGATCGGT CTGACCCCGG GGGAGTCA 48

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

AGAGAATTCT AATACGACTC ACTATAGGAT ACGATCGGTC TGAC

44

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TGTACAGGGG ACCCGCGAAC GGATCCAATT

30

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGCGAATTC ATGCATAGGG GACCCGCGAA CGGATC

36

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CGTCGACTAC GGGATTCTGG

20

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs

27

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CAGAGGCAGT ACTCCGTCTG

20

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AGTCGACGGG ATTCTTGCTT

20

(2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GAAGGTGTGC GAGAGGAC

18

(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 44 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

AGAGAATTCT AATACGACTC ACTATAGGAT ACGATGGGTC TGAC

44

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGATCTGCTG CAGGGGGCCC CCGCAGGCCA AGG

33

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CTTGAGACTC TTGTTCTCTA CTCC

24

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ATACAGCAA GATCTCGGG

19

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2827 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 112..2745

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GGATACGATG GGTCTGACCC TCTGGGAGTC ACGAATTAAC GTGGCTACTA GGGGCGATAC	60
CCGCCGCTGG CCGCCACGTT AGTGGCTCCT CTTCTTGATG ATTCTGCCAC C ATG AGT	117
Met Ser	
1	
GAC ATT TTC AAC AGT CCA CAG GCG CGA AGC ACG ATC TCA GCA GCG TTC	165
Asp Ile Phe Asn Ser Pro Gln Ala Arg Ser Thr Ile Ser Ala Ala Phe	
5 10 15	
GGC ATA AAG CCT ACT GCT GGA CAA GAC GTG GAA GAA CTC TTG ATC CCT	213
Gly Ile Lys Pro Thr Ala Gly Gln Asp Val Glu Glu Leu Leu Ile Pro	
20 25 30	
AAA GTT TGG GTG CCA CCT GAG GAT CCG CTT GCC AGC CCT AGT CGA CTG	261
Lys Val Trp Val Pro Pro Glu Asp Pro Leu Ala Ser Pro Ser Arg Leu	
35 40 45 50	
GCA AAG TTC CTC AGA GAG AAC GGC TAC AAA GTT TTG CAG CCA CGG TCT	309
Ala Lys Phe Leu Arg Glu Asn Gly Tyr Lys Val Leu Gln Pro Arg Ser	
55 60 65	
CTG CCC GAG AAT GAG GAG TAT GAG ACC GAC CAA ATA CTC CCA GAC TTA	357
Leu Pro Glu Asn Glu Glu Tyr Glu Thr Asp Gln Ile Leu Pro Asp Leu	
70 75 80	
GCA TGG ATG CGA CAG ATA GAA GGG GCT GTT TTA AAA CCC ACT CTA TCT	405
Ala Trp Met Arg Gln Ile Glu Gly Ala Val Leu Lys Pro Thr Leu Ser	
85 90 95	
CTC CCT ATT GGA GAT CAG GAG TAC TTC CCA AAG TAC TAC CCA ACA CAT	453
Leu Pro Ile Gly Asp Gln Glu Tyr Phe Pro Lys Tyr Tyr Pro Thr His	
100 105 110	
CGC CCT AGC AAG GAG AAG CCC AAT GCG TAC CCG CCA GAC ATC GCA CTA	501
Arg Pro Ser Lys Glu Lys Pro Asn Ala Tyr Pro Pro Asp Ile Ala Leu	
115 120 125 130	

30

CTC AAG CAG ATG ATT TAC CTG TTT CTC CAG GTT CCA GAG GCC AAC GAG	549
Leu Lys Gln Met Ile Tyr Leu Phe Leu Gln Val Pro Glu Ala Asn Glu	
135 140 145	
GGC CTA AAG GAT GAA GTA ACC CTC TTG ACC CAA AAC ATA AGG GAC AAG	597
Gly Leu Lys Asp Glu Val Thr Leu Leu Thr Gln Asn Ile Arg Asp Lys	
150 155 160	
GCC TAT GGA AGT GGG ACC TAC ATG GGA CAA GCA AAT CGA CTT GTG GCC	645
Ala Tyr Gly Ser Gly Thr Tyr Met Gly Gln Ala Asn Arg Leu Val Ala	
165 170 175	
ATG AAG GAG GTC GCC ACT GGA AGA AAC CCA AAC AAG GAT CCT CTA AAG	693
Met Lys Glu Val Ala Thr Gly Arg Asn Pro Asn Lys Asp Pro Leu Lys	
180 185 190	
CTT GGG TAC ACT TTT GAG AGC ATC GCG CAG CTA CTT GAC ATC ACA CTA	741
Leu Gly Tyr Thr Phe Glu Ser Ile Ala Gln Leu Leu Asp Ile Thr Leu	
195 200 205 210	
CCG GTA GGC CCA CCC GGT GAG GAT GAC AAG CCC TGG GTG CCA CTC ACA	789
Pro Val Gly Pro Pro Gly Glu Asp Asp Lys Pro Trp Val Pro Leu Thr	
215 220 225	
AGA GTG CCG TCA CGG ATG TTG GTG CTG ACG GGA GAC GTA GAT GGC GAC	837
Arg Val Pro Ser Arg Met Leu Val Leu Thr Gly Asp Val Asp Gly Asp	
230 235 240	
TTT GAG GTT GAA GAT TAC CTT CCC AAA ATC AAC CTC AAG TCA TCA AGT	885
Phe Glu Val Glu Asp Tyr Leu Pro Lys Ile Asn Leu Lys Ser Ser Ser	
245 250 255	
GGA CTA CCA TAT GTA GGT CGC ACC AAA GGA GAG ACA ATT GGC GAG ATG	933
Gly Leu Pro Tyr Val Gly Arg Thr Lys Gly Glu Thr Ile Gly Glu Met	
260 265 270	
ATA GCT ATC TCA AAC CAG TTT CTC AGA GAG CTA TCA ACA CTG TTG AAG	981
Ile Ala Ile Ser Asn Gln Phe Leu Arg Glu Leu Ser Thr Leu Leu Lys	
275 280 285 290	
CAA GGT GCA GGG ACA AAG GGG TCA AAC AAG AAG AAG CTA CTC AGC ATG	1029
Gln Gly Ala Gly Thr Lys Gly Ser Asn Lys Lys Lys Leu Leu Ser Met	
295 300 305	
TTA AGT GAC TAT TGG TAC TTA TCA TGC GGG CTT TTG TTT CCA AAG GCT	1077
Leu Ser Asp Tyr Trp Tyr Leu Ser Cys Gly Leu Leu Phe Pro Lys Ala	
310 315 320	
GAA AGG TAC GAC AAA AGT ACA TGG CTC ACC AAG ACC CGG AAC ATA TGG	1125
Glu Arg Tyr Asp Lys Ser Thr Trp Leu Thr Lys Thr Arg Asn Ile Trp	
325 330 335	

TCA	GCT	CCA	TCC	CCA	ACA	CAC	CTC	ATG	ATC	TCT	ATG	ATC	ACC	TGG	CCC	1173
Ser	Ala	Pro	Ser	Pro	Thr	His	Leu	Met	Ile	Ser	Met	Ile	Thr	Trp	Pro	
340						345					350					
GTG	ATG	TCC	AAC	AGC	CCA	AAT	AAC	GTG	TTG	AAC	ATT	GAA	GGG	TGT	CCA	1221
Val	Met	Ser	Asn	Ser	Pro	Asn	Asn	Val	Leu	Asn	Ile	Glu	Gly	Cys	Pro	
355					360					365					370	
TCA	CTC	TAC	AAA	TTC	AAC	CCG	TTC	AGA	GGA	GGG	TTG	AAC	AGG	ATC	GTC	1269
Ser	Leu	Tyr	Lys	Phe	Asn	Pro	Phe	Arg	Gly	Gly	Leu	Asn	Arg	Ile	Val	
				375					380					385		
GAG	TGG	ATA	TTG	GCC	CCG	GAA	GAA	CCC	AAG	GCT	CTT	GTA	TAT	GCG	GAC	1317
Glu	Trp	Ile	Leu	Ala	Pro	Glu	Glu	Pro	Lys	Ala	Leu	Val	Tyr	Ala	Asp	
			390					395						400		
AAC	ATA	TAC	ATT	GTC	CAC	TCA	AAC	ACG	TGG	TAC	TCA	ATT	GAC	CTA	GAG	1365
Asn	Ile	Tyr	Ile	Val	His	Ser	Asn	Thr	Trp	Tyr	Ser	Ile	Asp	Leu	Glu	
		405					410						415			
AAG	GGT	GAG	GCA	AAC	TGC	ACT	CGC	CAA	CAC	ATG	CAA	GCC	GCA	ATG	TAC	1413
Lys	Gly	Glu	Ala	Asn	Cys	Thr	Arg	Gln	His	Met	Gln	Ala	Ala	Met	Tyr	
	420					425					430					
TAC	ATA	CTC	ACC	AGA	GGG	TGG	TCA	GAC	AAC	GGC	GAC	CCA	ATG	TTC	AAT	1461
Tyr	Ile	Leu	Thr	Arg	Gly	Trp	Ser	Asp	Asn	Gly	Asp	Pro	Met	Phe	Asn	
435					440					445					450	
CAA	ACA	TGG	GCC	ACC	TTT	GCC	ATG	AAC	ATT	GCC	CCT	GCT	CTA	GTG	GTG	1509
Gln	Thr	Trp	Ala	Thr	Phe	Ala	Met	Asn	Ile	Ala	Pro	Ala	Leu	Val	Val	
				455					460					465		
GAC	TCA	TCG	TGC	CTG	ATA	ATG	AAC	CTG	CAA	ATT	AAG	ACC	TAT	GGT	CAA	1557
Asp	Ser	Ser	Cys	Leu	Ile	Met	Asn	Leu	Gln	Ile	Lys	Thr	Tyr	Gly	Gln	
			470					475					480			
GGC	AGC	GGG	AAT	GCA	GCC	ACG	TTC	ATC	AAC	AAC	CAC	CTC	TTG	AGC	ACA	1605
Gly	Ser	Gly	Asn	Ala	Ala	Thr	Phe	Ile	Asn	Asn	His	Leu	Leu	Ser	Thr	
		485					490					495				
CTA	GTG	CTT	GAC	CAG	TGG	AAC	CTG	ATG	AGA	CAG	CCC	AGA	CCA	GAC	AGC	1653
Leu	Val	Leu	Asp	Gln	Trp	Asn	Leu	Met	Arg	Gln	Pro	Arg	Pro	Asp	Ser	
		500				505					510					
GAG	GAG	TTC	AAA	TCA	ATT	GAG	GAC	AAG	CTA	GGT	ATC	AAC	TTT	AAG	ATT	1701
Glu	Glu	Phe	Lys	Ser	Ile	Glu	Asp	Lys	Leu	Gly	Ile	Asn	Phe	Lys	Ile	
515					520					525					530	
GAG	AGG	TCC	ATT	GAT	GAT	ATC	AGG	GGC	AAG	CTG	AGA	CAG	CTT	GTC	CTC	1749
Glu	Arg	Ser	Ile	Asp	Asp	Ile	Arg	Gly	Lys	Leu	Arg	Gln	Leu	Val	Leu	
				535					540					545		

CTT GCA CAA CCA GGG TAC CTG AGT GGG GGG GTT GAA CCA GAA CAA TCC	1797
Leu Ala Gln Pro Gly Tyr Leu Ser Gly Gly Val Glu Pro Glu Gln Ser	
550 555 560	
AGC CCA ACT GTT GAG CTT GAC CTA CTA GGG TGG TCA GCT ACA TAC AGC	1845
Ser Pro Thr Val Glu Leu Asp Leu Leu Gly Trp Ser Ala Thr Tyr Ser	
565 570 575	
AAA GAT CTC GGG ATC TAT GTG CCG GTG CTT GAC AAG GAA CGC CTA TTT	1893
Lys Asp Leu Gly Ile Tyr Val Pro Val Leu Asp Lys Glu Arg Leu Phe	
580 585 590	
TGT TCT GCT GCG TAT CCC AAG GGA GTA GAG AAC AAG AGT CTC AAG TCC	1941
Cys Ser Ala Ala Tyr Pro Lys Gly Val Glu Asn Lys Ser Leu Lys Ser	
595 600 605 610	
AAA GTC GGG ATC GAG CAG GCA TAC AAG GTA GTC AGG TAT GAG GCG TTG	1989
Lys Val Gly Ile Glu Gln Ala Tyr Lys Val Val Arg Tyr Glu Ala Leu	
615 620 625	
AGG TTG GTA GGT GGT TGG AAC TAC CCA CTC CTG AAC AAA GCC TGC AAG	2037
Arg Leu Val Gly Gly Trp Asn Tyr Pro Leu Leu Asn Lys Ala Cys Lys	
630 635 640	
AAT AAC GCA GGC GCC GCT CGG CGG CAT CTG GAG GCC AAG GGG TTC CCA	2085
Asn Asn Ala Gly Ala Ala Arg Arg His Leu Glu Ala Lys Gly Phe Pro	
645 650 655	
CTC GAC GAG TTC CTA GCC GAG TGG TCT GAG CTG TCA GAG TTC GGT GAG	2133
Leu Asp Glu Phe Leu Ala Glu Trp Ser Glu Leu Ser Glu Phe Gly Glu	
660 665 670	
GCC TTC GAA GGC TTC AAT ATC AAG CTG ACC GTA ACA TCT GAG AGC CTA	2181
Ala Phe Glu Gly Phe Asn Ile Lys Leu Thr Val Thr Ser Glu Ser Leu	
675 680 685 690	
GCC GAA CTG AAC AAG CCA GTA CCC CCC AAG CCC CCA AAT GTC AAC AGA	2229
Ala Glu Leu Asn Lys Pro Val Pro Pro Lys Pro Pro Asn Val Asn Arg	
695 700 705	
CCA GTC AAC ACT GGG GGA CTC AAG GCA GTC AGC AAC GCC CTC AAG ACC	2277
Pro Val Asn Thr Gly Gly Leu Lys Ala Val Ser Asn Ala Leu Lys Thr	
710 715 720	
GGT CGG TAC AGG AAC GAA GCC GGA CTG AGT GGT CTC GTC CTT CTA GCC	2325
Gly Arg Tyr Arg Asn Glu Ala Gly Leu Ser Gly Leu Val Leu Leu Ala	
725 730 735	
ACA GCA AGA AGC CGT CTG CAA GAT GCA GTT AAG GCC AAG GCA GAA GCC	2373
Thr Ala Arg Ser Arg Leu Gln Asp Ala Val Lys Ala Lys Ala Glu Ala	
740 745 750	

33

GAG AAA CTC CAC AAG TCC AAG CCA GAC GAC CCC GAT GCA GAC TGG TTC	2421
Glu Lys Leu His Lys Ser Lys Pro Asp Asp Pro Asp Ala Asp Trp Phe	
755 760 765 770	
GAA AGA TCA GAA ACT CTG TCA GAC CTT CTG GAG AAA GCC GAC ATC GCC	2469
Glu Arg Ser Glu Thr Leu Ser Asp Leu Leu Glu Lys Ala Asp Ile Ala	
775 780 785	
AGC AAG GTC GCC CAC TCA GCA CTC GTG GAA ACA AGC GAC GCC CTT GAA	2517
Ser Lys Val Ala His Ser Ala Leu Val Glu Thr Ser Asp Ala Leu Glu	
790 795 800	
GCA GTT CAG TCG ACT TCC GTG TAC ACC CCC AAG TAC CCA GAA GTC AAG	2565
Ala Val Gln Ser Thr Ser Val Tyr Thr Pro Lys Tyr Pro Glu Val Lys	
805 810 815	
AAC CCA CAG ACC GCC TCC AAC CCC GTT GTT GGG CTC CAC CTG CCC GCC	2613
Asn Pro Gln Thr Ala Ser Asn Pro Val Val Gly Leu His Leu Pro Ala	
820 825 830	
AAG AGA GCC ACC GGT GTC CAG GCC GCT CTT CTC GGA GCA GGA ACG AGC	2661
Lys Arg Ala Thr Gly Val Gln Ala Ala Leu Leu Gly Ala Gly Thr Ser	
835 840 845 850	
AGA CCA ATG GGG ATG GAG GCC CCA ACA CGG TCC AAG AAC GCC GTG AAA	2709
Arg Pro Met Gly Met Glu Ala Pro Thr Arg Ser Lys Asn Ala Val Lys	
855 860 865	
ATG GCC AAA CGG CGG CAA CGC CAA AAG GAG AGC CGC TAACAGCCAT	2755
Met Ala Lys Arg Arg Gln Arg Gln Lys Glu Ser Arg	
870 875	
GATGGGAACC ACTCAAGAAG AGGACACTAA TCCCAGACCC CGTATCCCCG GCCTTCGCCT	2815
GCGGGGGCCC CC	2827

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 878 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Ser Asp Ile Phe Asn Ser Pro Gln Ala Arg Ser Thr Ile Ser Ala
1 5 10 15

Ala Phe Gly Ile Lys Pro Thr Ala Gly Gln Asp Val Glu Glu Leu Leu

34

20	25	30
Ile Pro Lys Val Trp Val Pro Pro Glu Asp Pro Leu Ala Ser Pro Ser		
35	40	45
Arg Leu Ala Lys Phe Leu Arg Glu Asn Gly Tyr Lys Val Leu Gln Pro		
50	55	60
Arg Ser Leu Pro Glu Asn Glu Glu Tyr Glu Thr Asp Gln Ile Leu Pro		
65	70	75
80		
Asp Leu Ala Trp Met Arg Gln Ile Glu Gly Ala Val Leu Lys Pro Thr		
85	90	95
Leu Ser Leu Pro Ile Gly Asp Gln Glu Tyr Phe Pro Lys Tyr Tyr Pro		
100	105	110
Thr His Arg Pro Ser Lys Glu Lys Pro Asn Ala Tyr Pro Pro Asp Ile		
115	120	125
Ala Leu Leu Lys Gln Met Ile Tyr Leu Phe Leu Gln Val Pro Glu Ala		
130	135	140
Asn Glu Gly Leu Lys Asp Glu Val Thr Leu Leu Thr Gln Asn Ile Arg		
145	150	155
160		
Asp Lys Ala Tyr Gly Ser Gly Thr Tyr Met Gly Gln Ala Asn Arg Leu		
165	170	175
Val Ala Met Lys Glu Val Ala Thr Gly Arg Asn Pro Asn Lys Asp Pro		
180	185	190
Leu Lys Leu Gly Tyr Thr Phe Glu Ser Ile Ala Gln Leu Leu Asp Ile		
195	200	205
Thr Leu Pro Val Gly Pro Pro Gly Glu Asp Asp Lys Pro Trp Val Pro		
210	215	220
Leu Thr Arg Val Pro Ser Arg Met Leu Val Leu Thr Gly Asp Val Asp		
225	230	235
240		
Gly Asp Phe Glu Val Glu Asp Tyr Leu Pro Lys Ile Asn Leu Lys Ser		
245	250	255
Ser Ser Gly Leu Pro Tyr Val Gly Arg Thr Lys Gly Glu Thr Ile Gly		
260	265	270
Glu Met Ile Ala Ile Ser Asn Gln Phe Leu Arg Glu Leu Ser Thr Leu		
275	280	285
Leu Lys Gln Gly Ala Gly Thr Lys Gly Ser Asn Lys Lys Lys Leu Leu		

290	295	300
Ser Met Leu Ser Asp Tyr Trp Tyr Leu Ser Cys Gly Leu Leu Phe Pro		
305	310	315 320
Lys Ala Glu Arg Tyr Asp Lys Ser Thr Trp Leu Thr Lys Thr Arg Asn		
	325	330 335
Ile Trp Ser Ala Pro Ser Pro Thr His Leu Met Ile Ser Met Ile Thr		
	340	345 350
Trp Pro Val Met Ser Asn Ser Pro Asn Asn Val Leu Asn Ile Glu Gly		
	355	360 365
Cys Pro Ser Leu Tyr Lys Phe Asn Pro Phe Arg Gly Gly Leu Asn Arg		
	370	375 380
Ile Val Glu Trp Ile Leu Ala Pro Glu Glu Pro Lys Ala Leu Val Tyr		
	385	390 395 400
Ala Asp Asn Ile Tyr Ile Val His Ser Asn Thr Trp Tyr Ser Ile Asp		
	405	410 415
Leu Glu Lys Gly Glu Ala Asn Cys Thr Arg Gln His Met Gln Ala Ala		
	420	425 430
Met Tyr Tyr Ile Leu Thr Arg Gly Trp Ser Asp Asn Gly Asp Pro Met		
	435	440 445
Phe Asn Gln Thr Trp Ala Thr Phe Ala Met Asn Ile Ala Pro Ala Leu		
	450	455 460
Val Val Asp Ser Ser Cys Leu Ile Met Asn Leu Gln Ile Lys Thr Tyr		
	465	470 475 480
Gly Gln Gly Ser Gly Asn Ala Ala Thr Phe Ile Asn Asn His Leu Leu		
	485	490 495
Ser Thr Leu Val Leu Asp Gln Trp Asn Leu Met Arg Gln Pro Arg Pro		
	500	505 510
Asp Ser Glu Glu Phe Lys Ser Ile Glu Asp Lys Leu Gly Ile Asn Phe		
	515	520 525
Lys Ile Glu Arg Ser Ile Asp Asp Ile Arg Gly Lys Leu Arg Gln Leu		
	530	535 540
Val Leu Leu Ala Gln Pro Gly Tyr Leu Ser Gly Gly Val Glu Pro Glu		
	545	550 555 560
Gln Ser Ser Pro Thr Val Glu Leu Asp Leu Leu Gly Trp Ser Ala Thr		

										565											570											575	
Tyr	Ser	Lys	Asp	Leu	Gly	Ile	Tyr	Val	Pro	Val	Leu	Asp	Lys	Glu	Arg																		
										580											585											590	
Leu	Phe	Cys	Ser	Ala	Ala	Tyr	Pro	Lys	Gly	Val	Glu	Asn	Lys	Ser	Leu																		
										595											600											605	
Lys	Ser	Lys	Val	Gly	Ile	Glu	Gln	Ala	Tyr	Lys	Val	Val	Arg	Tyr	Glu																		
										610											615											620	
Ala	Leu	Arg	Leu	Val	Gly	Gly	Trp	Asn	Tyr	Pro	Leu	Leu	Asn	Lys	Ala																		
										625											630											635	640
Cys	Lys	Asn	Asn	Ala	Gly	Ala	Ala	Arg	Arg	His	Leu	Glu	Ala	Lys	Gly																		
										645											650											655	
Phe	Pro	Leu	Asp	Glu	Phe	Leu	Ala	Glu	Trp	Ser	Glu	Leu	Ser	Glu	Phe																		
										660											665											670	
Gly	Glu	Ala	Phe	Glu	Gly	Phe	Asn	Ile	Lys	Leu	Thr	Val	Thr	Ser	Glu																		
										675											680											685	
Ser	Leu	Ala	Glu	Leu	Asn	Lys	Pro	Val	Pro	Pro	Lys	Pro	Pro	Asn	Val																		
										690											695											700	
Asn	Arg	Pro	Val	Asn	Thr	Gly	Gly	Leu	Lys	Ala	Val	Ser	Asn	Ala	Leu																		
										705											710											715	720
Lys	Thr	Gly	Arg	Tyr	Arg	Asn	Glu	Ala	Gly	Leu	Ser	Gly	Leu	Val	Leu																		
										725											730											735	
Leu	Ala	Thr	Ala	Arg	Ser	Arg	Leu	Gln	Asp	Ala	Val	Lys	Ala	Lys	Ala																		
										740											745											750	
Glu	Ala	Glu	Lys	Leu	His	Lys	Ser	Lys	Pro	Asp	Asp	Pro	Asp	Ala	Asp																		
										755											760											765	
Trp	Phe	Glu	Arg	Ser	Glu	Thr	Leu	Ser	Asp	Leu	Leu	Glu	Lys	Ala	Asp																		
										770											775											780	
Ile	Ala	Ser	Lys	Val	Ala	His	Ser	Ala	Leu	Val	Glu	Thr	Ser	Asp	Ala																		
										785											790											795	800
Leu	Glu	Ala	Val	Gln	Ser	Thr	Ser	Val	Tyr	Thr	Pro	Lys	Tyr	Pro	Glu																		
										805											810											815	
Val	Lys	Asn	Pro	Gln	Thr	Ala	Ser	Asn	Pro	Val	Val	Gly	Leu	His	Leu																		
										820											825											830	
Pro	Ala	Lys	Arg	Ala	Thr	Gly	Val	Gln	Ala	Ala	Leu	Leu	Gly	Ala	Gly																		

835	840	845
Thr Ser Arg Pro Met Gly Met Glu Ala Pro Thr Arg Ser Lys Asn Ala		
850	855	860
Val Lys Met Ala Lys Arg Arg Gln Arg Gln Lys Glu Ser Arg		
865	870	875

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3261 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 97..531

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GGATACGATC GGTCTGACCC CGGGGGAGTC ACCCGGGGAC AGGCCGTCAA GGCCTTGTTT	60
CAGGATGGGA CTCCTCCTTC TACAACGCTA TCATTG ATG GTT AGT AGA GAT CAG	114
Met Val Ser Arg Asp Gln	880
ACA AAC GAT CGC AGC GAT GAC AAA CCT GCA AGA TCA AAC CCA ACA GAT	162
Thr Asn Asp Arg Ser Asp Asp Lys Pro Ala Arg Ser Asn Pro Thr Asp	885 890 895 900
TGT TCC GTT CAT ACG GAG CCT TCT GAT GCC AAC AAC CGG ACC GGC GTC	210
Cys Ser Val His Thr Glu Pro Ser Asp Ala Asn Asn Arg Thr Gly Val	905 910 915
CAT TCC GGA CGA CAC CCT GGA GAA GCA CAC TCT CAG GTC AGA GAC CTC	258
His Ser Gly Arg His Pro Gly Glu Ala His Ser Gln Val Arg Asp Leu	920 925 930
GAC CTA CAA TTT GAC TGT GGG GGA CAC AGG GTC AGG GCT AAT TGT CTT	306
Asp Leu Gln Phe Asp Cys Gly Gly His Arg Val Arg Ala Asn Cys Leu	935 940 945
TTT CCC TGG ATT CCC TGG CTC AAT TGT GGG TGC TCA CTA CAC ACT GCA	354
Phe Pro Trp Ile Pro Trp Leu Asn Cys Gly Cys Ser Leu His Thr Ala	950 955 960

GGG CAA TGG GAA CTA CAA GTT CGA TCA GAT GCT CCT GAC TGC CCA GAA	402
Gly Gln Trp Glu Leu Gln Val Arg Ser Asp Ala Pro Asp Cys Pro Glu	
965 970 975 980	
CCT ACC GGC CAG TTA CAA CTA CTG CAG GCT AGT GAG TCG GAG TCT CAC	450
Pro Thr Gly Gln Leu Gln Leu Leu Gln Ala Ser Glu Ser Glu Ser His	
985 990 995	
AGT GAG GTC AAG CAC ACT TCC TGG TGG CGT TTA TGC ACT AAA CGG CAC	498
Ser Glu Val Lys His Thr Ser Trp Trp Arg Leu Cys Thr Lys Arg His	
1000 1005 1010	
CAT AAA CGC CGT GAC CTT CCA AGG AAG CCT GAG TGAAGTACATA GATGTTAGCT	551
His Lys Arg Arg Asp Leu Pro Arg Lys Pro Glu	
1015 1020	
ACAATGGGTT GATGTCTGCA ACAGCCAACA TCAACGACAA AATTGGGAAC GTCCTAGTAG	611
GGGAAGGGGT CACCGTCCTC AGCTTACCCA CATCATATGA TCTTGGGTAT GTGAGGCTTG	671
GTGACCCCAT TCCC GCAATA GGGCTTGACC CAAAATGGT AGCCACATGT GACAGCAGTG	731
ACAGGCCCAG AGTCTACACC ATAAGTGCAG CCGATGATTA CCAATTCTCA TCACAGTACC	791
AACCAGGTGG GGTAACAATC AACTGTCTCT CAGCCAACAT TGATGCCATC ACAAGCCTCA	851
GCGTTGGGGG AGAGCTCGTG TTTCAAACAA GCGTCCACGG CTTGTACTG GGC GCCACCA	911
TCTACCTCAT AGGCTTTGAT GGGACAACGG TAATCACCAG GGCTGTGGCC GCAAACAATG	971
GGCTGACGAC CGGCACCGAC AACCTTATGC CATTCAATCT TGTGATTCCA ACAACGAGA	1031
TAACCCAGCC AATCACATCC ATCAAAGTGG AGATAGTGAC CTCCAAAAGT GGTGGTCAGG	1091
CAGGGGATCA GATGTCATGG TCGGCAAGAG GGAGCCTAGC AGTGACGATC CATGGTGGCA	1151
ACTATCCAGG GGCCCTCCGT CCCGTCACGC TAGTGGCCTA CGAAAGAGTG GCAACAGGAT	1211
CCGTCGTTAC GGTGCTGGG GTGAGCAACT TCGAGCTGAT CCCAAATCCT GAACTAGCAA	1271
AGAACCTGGT TACAGAATAC GGCCGATTTG ACCCAGGAGC CATGAACTAC ACAAATTGA	1331
TACTGAGTGA GAGGGACCGT CTTGGCATCA AGACCGTCTG GCCAACAAGG GAGTACACTG	1391
ACTTTCGTGA ATACTTCATG GAGGTGGCCG ACCTCAACTC TCCCCTGAAG ATTGCAGGAG	1451
CATTCGGCTT CAAAGACATA ATCCGGGCCA TAAGGAGGAT AGCTGTGCCG GTGGTCTCCA	1511
CATTGTTCCC ACCTGCCGCT CCCCTAGCCC ATGCAATTGG GGAAGGTGTA GACTACCTGC	1571
TGGGCGATGA GGCACAGGCT GCTTCAGGAA CTGCTCGAGC CGCGTCAGGA AAAGCAAGAG	1631

CTGCCTCAGG CCGCATAAGG CAGCTGACTC TCGCCGCCGA CAAGGGGTAC GAGGTAGTCG 1691
CGAATCTATT CCAGGTGCCC CAGAATCCCG TAGTCGACGG GATTCTTGCT TCACCTGGGG 1751
TACTCCGCGG TGCACACAAC CTCGACTGCG TGTTAAGAGA GGGTGCCACG CTATTCCCTG 1811
TGGTTATTAC GACAGTGGAA GACGCCATGA CACCCAAAGC ATTGAACAGC AAAATGTTTG 1871
CTGTCATTGA AGGCGTGCGA GAAGACCTCC AACCTCCATC TCAAAGAGGA TCCTTCATAC 1931
GAACTCTCTC TGGACACAGA GTCTATGGAT ATGCTCCAGA TGGGGTACTT CCACTGGAGA 1991
CTGGGAGAGA CTACACCGTT GTCCCAATAG ATGATGTCTG GGACGACAGC ATTATGCTGT 2051
CCAAAGATCC CATACTCCT ATTGTGGGAA ACAGTGGAAA TCTAGCCATA GCTTACATGG 2111
ATGTGTTTTG ACCCAAAGTC CCAATCCATG TGGCTATGAC GGGAGCCCTC AATGCTTGTG 2171
GCGAGATTGA GAAAGTAAGC TTTAGAAGCA CCAAGCTCGC CACTGCACAC CGACTTGGCC 2231
TTAGGTTGGC TGGTCCCGGA GCATTCGATG TAAACACCGG GCCCAACTGG GCAACGTTCA 2291
TCAAACGTTT CCCTCACAAT CCACGCGACT GGGACAGGCT CCCCTACCTC AACCTACCAT 2351
ACCTTCCACC CAATGCAGGA CGCCAGTACC ACCTTGCCAT GGCTGCATCA GAGTTCAAAG 2411
AGACCCCCGA ACTCGAGAGT GCCGTCAGAG CAATGGAAGC AGCAGCCAAC GTGGACCCAC 2471
TATTCCAATC TGCACTCAGT GTGTTTCATG GGCTGGAAGA GAATGGGATT GTGACTGACA 2531
TGGCCAACTT CGCACTCAGC GACCCGAACG CCCATCGGAT GCGAAATTTT CTTGCAAACG 2591
CACCACAAGC AGGCAGCAAG TCGCAAAGGG CCAAGTACGG GACAGCAGGC TACGGAGTGG 2651
AGGCTCGGGG CCCACACCA GAGGAAGCAC AGAGGGAAAA AGACACACGG ATCTCAAAGA 2711
AGATGGAGAC CATGGGCATC TACTTTGCAA CACCAGAATG GGTAGCACTC AATGGGCACC 2771
GAGGGCCAAG CCCC GGCCAG CTAAAGTACT GGCAGAACAC ACGAGAAATA CCGGACCCAA 2831
ACGAGGACTA TCTAGACTAC GTGCATGCAG AGAAGAGCCG GTTGGCATCA GAAGAACAAA 2891
TCCTAAGGGC AGCTACGTCG ATCTACGGGG CTCCAGGACA GGCAGAGCCA CCCCAGCTT 2951
TCATAGACGA AGTTGCCAAA GTCTATGAAA TCAACCATGG ACGTGGCCCA AACCAAGAAC 3011
AGATGAAAGA TCTGCTCTTG ACTGCGATGG AGATGAAGCA TCGCAATCCC AGGCGGGCTC 3071
TACCAAAGCC CAAGCCAAAA CCAATGCTC CAACACAGAG ACCCCCTGGT CGGCTGGGCC 3131
GCTGGATCAG GACCGTCTCT GATGAGGACC TTGAGTGAGG CTCCTGGGAG TCTCCCGACA 3191

CCACCCGCGC AGGTGTGGAC ACCAATTCGG CCTTACAACA TCCCAAATTG GATCCGTTCC 3251
 CGGGTCCCCCT 3261

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 145 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met	Val	Ser	Arg	Asp	Gln	Thr	Asn	Asp	Arg	Ser	Asp	Asp	Lys	Pro	Ala	1	5	10	15
Arg	Ser	Asn	Pro	Thr	Asp	Cys	Ser	Val	His	Thr	Glu	Pro	Ser	Asp	Ala	20	25	30	
Asn	Asn	Arg	Thr	Gly	Val	His	Ser	Gly	Arg	His	Pro	Gly	Glu	Ala	His	35	40	45	
Ser	Gln	Val	Arg	Asp	Leu	Asp	Leu	Gln	Phe	Asp	Cys	Gly	Gly	His	Arg	50	55	60	
Val	Arg	Ala	Asn	Cys	Leu	Phe	Pro	Trp	Ile	Pro	Trp	Leu	Asn	Cys	Gly	65	70	75	80
Cys	Ser	Leu	His	Thr	Ala	Gly	Gln	Trp	Glu	Leu	Gln	Val	Arg	Ser	Asp	85	90	95	
Ala	Pro	Asp	Cys	Pro	Glu	Pro	Thr	Gly	Gln	Leu	Gln	Leu	Leu	Gln	Ala	100	105	110	
Ser	Glu	Ser	Glu	Ser	His	Ser	Glu	Val	Lys	His	Thr	Ser	Trp	Trp	Arg	115	120	125	
Leu	Cys	Thr	Lys	Arg	His	His	Lys	Arg	Arg	Asp	Leu	Pro	Arg	Lys	Pro	130	135	140	
Glu																145			

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3261 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 131..3166

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

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GGATACGATC GGTCTGACCC CGGGGGAGTC ACCCGGGGAC AGGCCGTCAA GGCCTTGTTT    60
CAGGATGGGA CTCCTCCTTC TACAACGCTA TCATTGATGG TTAGTAGAGA TCAGACAAAC    120
GATCGCAGCG ATG ACA AAC CTG CAA GAT CAA ACC CAA CAG ATT GTT CCG    169
      Met Thr Asn Leu Gln Asp Gln Thr Gln Gln Ile Val Pro
                        150                        155

TTC ATA CGG AGC CTT CTG ATG CCA ACA ACC GGA CCG GCG TCC ATT CCG    217
Phe Ile Arg Ser Leu Leu Met Pro Thr Thr Gly Pro Ala Ser Ile Pro
      160                        165                        170

GAC GAC ACC CTG GAG AAG CAC ACT CTC AGG TCA GAG ACC TCG ACC TAC    265
Asp Asp Thr Leu Glu Lys His Thr Leu Arg Ser Glu Thr Ser Thr Tyr
      175                        180                        185                        190

AAT TTG ACT GTG GGG GAC ACA GGG TCA GGG CTA ATT GTC TTT TTC CCT    313
Asn Leu Thr Val Gly Asp Thr Gly Ser Gly Leu Ile Val Phe Phe Pro
                        195                        200                        205

GGA TTC CCT GGC TCA ATT GTG GGT GCT CAC TAC ACA CTG CAG GGC AAT    361
Gly Phe Pro Gly Ser Ile Val Gly Ala His Tyr Thr Leu Gln Gly Asn
                        210                        215                        220

GGG AAC TAC AAG TTC GAT CAG ATG CTC CTG ACT GCC CAG AAC CTA CCG    409
Gly Asn Tyr Lys Phe Asp Gln Met Leu Leu Thr Ala Gln Asn Leu Pro
                        225                        230                        235

GCC AGT TAC AAC TAC TGC AGG CTA GTG AGT CGG AGT CTC ACA GTG AGG    457
Ala Ser Tyr Asn Tyr Cys Arg Leu Val Ser Arg Ser Leu Thr Val Arg
                        240                        245                        250

TCA AGC ACA CTT CCT GGT GGC GTT TAT GCA CTA AAC GGC ACC ATA AAC    505
Ser Ser Thr Leu Pro Gly Gly Val Tyr Ala Leu Asn Gly Thr Ile Asn
      255                        260                        265                        270

GCC GTG ACC TTC CAA GGA AGC CTG AGT GAA CTG ACA GAT GTT AGC TAC    553

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Ala	Val	Thr	Phe	Gln	Gly	Ser	Leu	Ser	Glu	Leu	Thr	Asp	Val	Ser	Tyr	
				275					280					285		
AAT	GGG	TTG	ATG	TCT	GCA	ACA	GCC	AAC	ATC	AAC	GAC	AAA	ATT	GGG	AAC	601
Asn	Gly	Leu	Met	Ser	Ala	Thr	Ala	Asn	Ile	Asn	Asp	Lys	Ile	Gly	Asn	
			290					295					300			
GTC	CTA	GTA	GGG	GAA	GGG	GTC	ACC	GTC	CTC	AGC	TTA	CCC	ACA	TCA	TAT	649
Val	Leu	Val	Gly	Glu	Gly	Val	Thr	Val	Leu	Ser	Leu	Pro	Thr	Ser	Tyr	
		305					310					315				
GAT	CTT	GGG	TAT	GTG	AGG	CTT	GGT	GAC	CCC	ATT	CCC	GCA	ATA	GGG	CTT	697
Asp	Leu	Gly	Tyr	Val	Arg	Leu	Gly	Asp	Pro	Ile	Pro	Ala	Ile	Gly	Leu	
	320					325					330					
GAC	CCA	AAA	ATG	GTA	GCC	ACA	TGT	GAC	AGC	AGT	GAC	AGG	CCC	AGA	GTC	745
Asp	Pro	Lys	Met	Val	Ala	Thr	Cys	Asp	Ser	Ser	Asp	Arg	Pro	Arg	Val	
335					340				345						350	
TAC	ACC	ATA	ACT	GCA	GCC	GAT	GAT	TAC	CAA	TTC	TCA	TCA	CAG	TAC	CAA	793
Tyr	Thr	Ile	Thr	Ala	Ala	Asp	Asp	Tyr	Gln	Phe	Ser	Ser	Gln	Tyr	Gln	
				355					360					365		
CCA	GGT	GGG	GTA	ACA	ATC	ACA	CTG	TTC	TCA	GCC	AAC	ATT	GAT	GCC	ATC	841
Pro	Gly	Gly	Val	Thr	Ile	Thr	Leu	Phe	Ser	Ala	Asn	Ile	Asp	Ala	Ile	
			370					375					380			
ACA	AGC	CTC	AGC	GTT	GGG	GGA	GAG	CTC	GTG	TTT	CAA	ACA	AGC	GTC	CAC	889
Thr	Ser	Leu	Ser	Val	Gly	Gly	Glu	Leu	Val	Phe	Gln	Thr	Ser	Val	His	
		385					390					395				
GGC	CTT	GTA	CTG	GGC	GCC	ACC	ATC	TAC	CTC	ATA	GGC	TTT	GAT	GGG	ACA	937
Gly	Leu	Val	Leu	Gly	Ala	Thr	Ile	Tyr	Leu	Ile	Gly	Phe	Asp	Gly	Thr	
	400					405					410					
ACG	GTA	ATC	ACC	AGG	GCT	GTG	GCC	GCA	AAC	AAT	GGG	CTG	ACG	ACC	GGC	985
Thr	Val	Ile	Thr	Arg	Ala	Val	Ala	Ala	Asn	Asn	Gly	Leu	Thr	Thr	Gly	
415					420				425						430	
ACC	GAC	AAC	CTT	ATG	CCA	TTC	AAT	CTT	GTG	ATT	CCA	ACA	AAC	GAG	ATA	1033
Thr	Asp	Asn	Leu	Met	Pro	Phe	Asn	Leu	Val	Ile	Pro	Thr	Asn	Glu	Ile	
				435					440					445		
ACC	CAG	CCA	ATC	ACA	TCC	ATC	AAA	CTG	GAG	ATA	GTG	ACC	TCC	AAA	AGT	1081
Thr	Gln	Pro	Ile	Thr	Ser	Ile	Lys	Leu	Glu	Ile	Val	Thr	Ser	Lys	Ser	
			450					455					460			
GGT	GGT	CAG	GCA	GGG	GAT	CAG	ATG	TCA	TGG	TCG	GCA	AGA	GGG	AGC	CTA	1129
Gly	Gly	Gln	Ala	Gly	Asp	Gln	Met	Ser	Trp	Ser	Ala	Arg	Gly	Ser	Leu	
		465					470					475				

GCA	GTG	ACG	ATC	CAT	GGT	GGC	AAC	TAT	CCA	GGG	GCC	CTC	CGT	CCC	GTC	1177
Ala	Val	Thr	Ile	His	Gly	Gly	Asn	Tyr	Pro	Gly	Ala	Leu	Arg	Pro	Val	
480						485					490					
ACG	CTA	GTG	GCC	TAC	GAA	AGA	GTG	GCA	ACA	GGA	TCC	GTC	GTT	ACG	GTC	1225
Thr	Leu	Val	Ala	Tyr	Glu	Arg	Val	Ala	Thr	Gly	Ser	Val	Val	Thr	Val	
495					500					505					510	
GCT	GGG	GTG	AGC	AAC	TTC	GAG	CTG	ATC	CCA	AAT	CCT	GAA	CTA	GCA	AAG	1273
Ala	Gly	Val	Ser	Asn	Phe	Glu	Leu	Ile	Pro	Asn	Pro	Glu	Leu	Ala	Lys	
				515					520					525		
AAC	CTG	GTT	ACA	GAA	TAC	GGC	CGA	TTT	GAC	CCA	GGA	GCC	ATG	AAC	TAC	1321
Asn	Leu	Val	Thr	Glu	Tyr	Gly	Arg	Phe	Asp	Pro	Gly	Ala	Met	Asn	Tyr	
			530					535					540			
ACA	AAA	TTG	ATA	CTG	AGT	GAG	AGG	GAC	CGT	CTT	GGC	ATC	AAG	ACC	GTC	1369
Thr	Lys	Leu	Ile	Leu	Ser	Glu	Arg	Asp	Arg	Leu	Gly	Ile	Lys	Thr	Val	
		545					550					555				
TGG	CCA	ACA	AGG	GAG	TAC	ACT	GAC	TTT	CGT	GAA	TAC	TTC	ATG	GAG	GTG	1417
Trp	Pro	Thr	Arg	Glu	Tyr	Thr	Asp	Phe	Arg	Glu	Tyr	Phe	Met	Glu	Val	
	560					565					570					
GCC	GAC	CTC	AAC	TCT	CCC	CTG	AAG	ATT	GCA	GGA	GCA	TTC	GGC	TTC	AAA	1465
Ala	Asp	Leu	Asn	Ser	Pro	Leu	Lys	Ile	Ala	Gly	Ala	Phe	Gly	Phe	Lys	
575					580					585					590	
GAC	ATA	ATC	CGG	GCC	ATA	AGG	AGG	ATA	GCT	GTG	CCG	GTG	GTC	TCC	ACA	1513
Asp	Ile	Ile	Arg	Ala	Ile	Arg	Arg	Ile	Ala	Val	Pro	Val	Val	Ser	Thr	
				595					600					605		
TTG	TTC	CCA	CCT	GCC	GCT	CCC	CTA	GCC	CAT	GCA	ATT	GGG	GAA	GGT	GTA	1561
Leu	Phe	Pro	Pro	Ala	Ala	Pro	Leu	Ala	His	Ala	Ile	Gly	Glu	Gly	Val	
			610					615					620			
GAC	TAC	CTG	CTG	GGC	GAT	GAG	GCA	CAG	GCT	GCT	TCA	GGA	ACT	GCT	CGA	1609
Asp	Tyr	Leu	Leu	Gly	Asp	Glu	Ala	Gln	Ala	Ala	Ser	Gly	Thr	Ala	Arg	
		625					630					635				
GCC	GCG	TCA	GGA	AAA	GCA	AGA	GCT	GCC	TCA	GGC	CGC	ATA	AGG	CAG	CTG	1657
Ala	Ala	Ser	Gly	Lys	Ala	Arg	Ala	Ala	Ser	Gly	Arg	Ile	Arg	Gln	Leu	
	640					645					650					
ACT	CTC	GCC	GCC	GAC	AAG	GGG	TAC	GAG	GTA	GTC	GCG	AAT	CTA	TTC	CAG	1705
Thr	Leu	Ala	Ala	Asp	Lys	Gly	Tyr	Glu	Val	Val	Ala	Asn	Leu	Phe	Gln	
655					660					665					670	
GTG	CCC	CAG	AAT	CCC	GTA	GTC	GAC	GGG	ATT	CTT	GCT	TCA	CCT	GGG	GTA	1753
Val	Pro	Gln	Asn	Pro	Val	Val	Asp	Gly	Ile	Leu	Ala	Ser	Pro	Gly	Val	
				675					680					685		

CTC CGC GGT GCA CAC AAC CTC GAC TGC GTG TTA AGA GAG GGT GCC ACG Leu Arg Gly Ala His Asn Leu Asp Cys Val Leu Arg Glu Gly Ala Thr 690 695 700	1801
CTA TTC CCT GTG GTT ATT ACG ACA GTG GAA GAC GCC ATG ACA CCC AAA Leu Phe Pro Val Val Ile Thr Thr Val Glu Asp Ala Met Thr Pro Lys 705 710 715	1849
GCA TTG AAC AGC AAA ATG TTT GCT GTC ATT GAA GGC GTG CGA GAA GAC Ala Leu Asn Ser Lys Met Phe Ala Val Ile Glu Gly Val Arg Glu Asp 720 725 730	1897
CTC CAA CCT CCA TCT CAA AGA GGA TCC TTC ATA CGA ACT CTC TCT GGA Leu Gln Pro Pro Ser Gln Arg Gly Ser Phe Ile Arg Thr Leu Ser Gly 735 740 745	1945
CAC AGA GTC TAT GGA TAT GCT CCA GAT GGG GTA CTT CCA CTG GAG ACT His Arg Val Tyr Gly Tyr Ala Pro Asp Gly Val Leu Pro Leu Glu Thr 755 760 765	1993
GGG AGA GAC TAC ACC GTT GTC CCA ATA GAT GAT GTC TGG GAC GAC AGC Gly Arg Asp Tyr Thr Val Val Pro Ile Asp Asp Val Trp Asp Asp Ser 770 775 780	2041
ATT ATG CTG TCC AAA GAT CCC ATA CCT CCT ATT GTG GGA AAC AGT GGA Ile Met Leu Ser Lys Asp Pro Ile Pro Pro Ile Val Gly Asn Ser Gly 785 790 795	2089
AAT CTA GCC ATA GCT TAC ATG GAT GTG TTT CGA CCC AAA GTC CCA ATC Asn Leu Ala Ile Ala Tyr Met Asp Val Phe Arg Pro Lys Val Pro Ile 800 805 810	2137
CAT GTG GCT ATG ACG GGA GCC CTC AAT GCT TGT GGC GAG ATT GAG AAA His Val Ala Met Thr Gly Ala Leu Asn Ala Cys Gly Glu Ile Glu Lys 815 820 825 830	2185
GTA AGC TTT AGA AGC ACC AAG CTC GCC ACT GCA CAC CGA CTT GGC CTT Val Ser Phe Arg Ser Thr Lys Leu Ala Thr Ala His Arg Leu Gly Leu 835 840 845	2233
AGG TTG GCT GGT CCC GGA GCA TTC GAT GTA AAC ACC GGG CCC AAC TGG Arg Leu Ala Gly Pro Gly Ala Phe Asp Val Asn Thr Gly Pro Asn Trp 850 855 860	2281
GCA ACG TTC ATC AAA CGT TTC CCT CAC AAT CCA CGC GAC TGG GAC AGG Ala Thr Phe Ile Lys Arg Phe Pro His Asn Pro Arg Asp Trp Asp Arg 865 870 875	2329
CTC CCC TAC CTC AAC CTA CCA TAC CTT CCA CCC AAT GCA GGA CGC CAG Leu Pro Tyr Leu Asn Leu Pro Tyr Leu Pro Pro Asn Ala Gly Arg Gln 880 885 890	2377

45

TAC	CAC	CTT	GCC	ATG	GCT	GCA	TCA	GAG	TTC	AAA	GAG	ACC	CCC	GAA	CTC	2425
Tyr	His	Leu	Ala	Met	Ala	Ala	Ser	Glu	Phe	Lys	Glu	Thr	Pro	Glu	Leu	
895					900					905					910	
GAG	AGT	GCC	GTC	AGA	GCA	ATG	GAA	GCA	GCA	GCC	AAC	GTG	GAC	CCA	CTA	2473
Glu	Ser	Ala	Val	Arg	Ala	Met	Glu	Ala	Ala	Ala	Asn	Val	Asp	Pro	Leu	
				915					920						925	
TTC	CAA	TCT	GCA	CTC	AGT	GTG	TTC	ATG	TGG	CTG	GAA	GAG	AAT	GGG	ATT	2521
Phe	Gln	Ser	Ala	Leu	Ser	Val	Phe	Met	Trp	Leu	Glu	Glu	Asn	Gly	Ile	
			930					935						940		
GTG	ACT	GAC	ATG	GCC	AAC	TTC	GCA	CTC	AGC	GAC	CCG	AAC	GCC	CAT	CGG	2569
Val	Thr	Asp	Met	Ala	Asn	Phe	Ala	Leu	Ser	Asp	Pro	Asn	Ala	His	Arg	
		945					950					955				
ATG	CGA	AAT	TTT	CTT	GCA	AAC	GCA	CCA	CAA	GCA	GGC	AGC	AAG	TCG	CAA	2617
Met	Arg	Asn	Phe	Leu	Ala	Asn	Ala	Pro	Gln	Ala	Gly	Ser	Lys	Ser	Gln	
	960					965					970					
AGG	GCC	AAG	TAC	GGG	ACA	GCA	GGC	TAC	GGA	GTG	GAG	GCT	CGG	GGC	CCC	2665
Arg	Ala	Lys	Tyr	Gly	Thr	Ala	Gly	Tyr	Gly	Val	Glu	Ala	Arg	Gly	Pro	
975					980				985						990	
ACA	CCA	GAG	GAA	GCA	CAG	AGG	GAA	AAA	GAC	ACA	CGG	ATC	TCA	AAG	AAG	2713
Thr	Pro	Glu	Glu	Ala	Gln	Arg	Glu	Lys	Asp	Thr	Arg	Ile	Ser	Lys	Lys	
				995					1000						1005	
ATG	GAG	ACC	ATG	GGC	ATC	TAC	TTT	GCA	ACA	CCA	GAA	TGG	GTA	GCA	CTC	2761
Met	Glu	Thr	Met	Gly	Ile	Tyr	Phe	Ala	Thr	Pro	Glu	Trp	Val	Ala	Leu	
			1010					1015					1020			
AAT	GGG	CAC	CGA	GGG	CCA	AGC	CCC	GGC	CAG	CTA	AAG	TAC	TGG	CAG	AAC	2809
Asn	Gly	His	Arg	Gly	Pro	Ser	Pro	Gly	Gln	Leu	Lys	Tyr	Trp	Gln	Asn	
		1025					1030					1035				
ACA	CGA	GAA	ATA	CCG	GAC	CCA	AAC	GAG	GAC	TAT	CTA	GAC	TAC	GTG	CAT	2857
Thr	Arg	Glu	Ile	Pro	Asp	Pro	Asn	Glu	Asp	Tyr	Leu	Asp	Tyr	Val	His	
		1040				1045					1050					
GCA	GAG	AAG	AGC	CGG	TTG	GCA	TCA	GAA	GAA	CAA	ATC	CTA	AGG	GCA	GCT	2905
Ala	Glu	Lys	Ser	Arg	Leu	Ala	Ser	Glu	Glu	Gln	Ile	Leu	Arg	Ala	Ala	
1055					1060					1065					1070	
ACG	TCG	ATC	TAC	GGG	GCT	CCA	GGA	CAG	GCA	GAG	CCA	CCC	CAA	GCT	TTC	2953
Thr	Ser	Ile	Tyr	Gly	Ala	Pro	Gly	Gln	Ala	Glu	Pro	Pro	Gln	Ala	Phe	
				1075				1080						1085		
ATA	GAC	GAA	GTT	GCC	AAA	GTC	TAT	GAA	ATC	AAC	CAT	GGA	CGT	GGC	CCA	3001
Ile	Asp	Glu	Val	Ala	Lys	Val	Tyr	Glu	Ile	Asn	His	Gly	Arg	Gly	Pro	
			1090					1095						1100		

46

AAC CAA GAA CAG ATG AAA GAT CTG CTC TTG ACT GCG ATG GAG ATG AAG 3049
 Asn Gln Glu Gln Met Lys Asp Leu Leu Leu Thr Ala Met Glu Met Lys
 1105 1110 1115

CAT CGC AAT CCC AGG CGG GCT CTA CCA AAG CCC AAG CCA AAA CCC AAT 3097
 His Arg Asn Pro Arg Arg Ala Leu Pro Lys Pro Lys Pro Lys Pro Asn
 1120 1125 1130

GCT CCA ACA CAG AGA CCC CCT GGT CGG CTG GGC CGC TGG ATC AGG ACC 3145
 Ala Pro Thr Gln Arg Pro Pro Gly Arg Leu Gly Arg Trp Ile Arg Thr
 1135 1140 1145 1150

GTC TCT GAT GAG GAC CTT GAG TGAGGCTCCT GGGAGTCTCC CGACACCACC 3196
 Val Ser Asp Glu Asp Leu Glu
 1155

CGCGCAGGTG TGGACACCAA TTCGGCCTTA CAACATCCCA AATTGGATCC GTTCGCGGGT 3256
 CCCCT 3261

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1012 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Thr Asn Leu Gln Asp Gln Thr Gln Gln Ile Val Pro Phe Ile Arg
 1 5 10 15

Ser Leu Leu Met Pro Thr Thr Gly Pro Ala Ser Ile Pro Asp Asp Thr
 20 25 30

Leu Glu Lys His Thr Leu Arg Ser Glu Thr Ser Thr Tyr Asn Leu Thr
 35 40 45

Val Gly Asp Thr Gly Ser Gly Leu Ile Val Phe Phe Pro Gly Phe Pro
 50 55 60

Gly Ser Ile Val Gly Ala His Tyr Thr Leu Gln Gly Asn Gly Asn Tyr
 65 70 75 80

Lys Phe Asp Gln Met Leu Leu Thr Ala Gln Asn Leu Pro Ala Ser Tyr
 85 90 95

Asn Tyr Cys Arg Leu Val Ser Arg Ser Leu Thr Val Arg Ser Ser Thr
 100 105 110

Leu Pro Gly Gly Val Tyr Ala Leu Asn Gly Thr Ile Asn Ala Val Thr
 115 120 125
 Phe Gln Gly Ser Leu Ser Glu Leu Thr Asp Val Ser Tyr Asn Gly Leu
 130 135 140
 Met Ser Ala Thr Ala Asn Ile Asn Asp Lys Ile Gly Asn Val Leu Val
 145 150 155 160
 Gly Glu Gly Val Thr Val Leu Ser Leu Pro Thr Ser Tyr Asp Leu Gly
 165 170 175
 Tyr Val Arg Leu Gly Asp Pro Ile Pro Ala Ile Gly Leu Asp Pro Lys
 180 185 190
 Met Val Ala Thr Cys Asp Ser Ser Asp Arg Pro Arg Val Tyr Thr Ile
 195 200 205
 Thr Ala Ala Asp Asp Tyr Gln Phe Ser Ser Gln Tyr Gln Pro Gly Gly
 210 215 220
 Val Thr Ile Thr Leu Phe Ser Ala Asn Ile Asp Ala Ile Thr Ser Leu
 225 230 235 240
 Ser Val Gly Gly Glu Leu Val Phe Gln Thr Ser Val His Gly Leu Val
 245 250 255
 Leu Gly Ala Thr Ile Tyr Leu Ile Gly Phe Asp Gly Thr Thr Val Ile
 260 265 270
 Thr Arg Ala Val Ala Ala Asn Asn Gly Leu Thr Thr Gly Thr Asp Asn
 275 280 285
 Leu Met Pro Phe Asn Leu Val Ile Pro Thr Asn Glu Ile Thr Gln Pro
 290 295 300
 Ile Thr Ser Ile Lys Leu Glu Ile Val Thr Ser Lys Ser Gly Gly Gln
 305 310 315 320
 Ala Gly Asp Gln Met Ser Trp Ser Ala Arg Gly Ser Leu Ala Val Thr
 325 330 335
 Ile His Gly Gly Asn Tyr Pro Gly Ala Leu Arg Pro Val Thr Leu Val
 340 345 350
 Ala Tyr Glu Arg Val Ala Thr Gly Ser Val Val Thr Val Ala Gly Val
 355 360 365
 Ser Asn Phe Glu Leu Ile Pro Asn Pro Glu Leu Ala Lys Asn Leu Val
 370 375 380
 Thr Glu Tyr Gly Arg Phe Asp Pro Gly Ala Met Asn Tyr Thr Lys Leu

385		390		395		400
Ile Leu Ser Glu Arg Asp Arg Leu Gly Ile Lys Thr Val Trp Pro Thr						
	405		410		415	
Arg Glu Tyr Thr Asp Phe Arg Glu Tyr Phe Met Glu Val Ala Asp Leu						
	420		425		430	
Asn Ser Pro Leu Lys Ile Ala Gly Ala Phe Gly Phe Lys Asp Ile Ile						
	435		440		445	
Arg Ala Ile Arg Arg Ile Ala Val Pro Val Val Ser Thr Leu Phe Pro						
	450		455		460	
Pro Ala Ala Pro Leu Ala His Ala Ile Gly Glu Gly Val Asp Tyr Leu						
	465		470		475	480
Leu Gly Asp Glu Ala Gln Ala Ala Ser Gly Thr Ala Arg Ala Ala Ser						
	485		490		495	
Gly Lys Ala Arg Ala Ala Ser Gly Arg Ile Arg Gln Leu Thr Leu Ala						
	500		505		510	
Ala Asp Lys Gly Tyr Glu Val Val Ala Asn Leu Phe Gln Val Pro Gln						
	515		520		525	
Asn Pro Val Val Asp Gly Ile Leu Ala Ser Pro Gly Val Leu Arg Gly						
	530		535		540	
Ala His Asn Leu Asp Cys Val Leu Arg Glu Gly Ala Thr Leu Phe Pro						
	545		550		555	560
Val Val Ile Thr Thr Val Glu Asp Ala Met Thr Pro Lys Ala Leu Asn						
	565		570		575	
Ser Lys Met Phe Ala Val Ile Glu Gly Val Arg Glu Asp Leu Gln Pro						
	580		585		590	
Pro Ser Gln Arg Gly Ser Phe Ile Arg Thr Leu Ser Gly His Arg Val						
	595		600		605	
Tyr Gly Tyr Ala Pro Asp Gly Val Leu Pro Leu Glu Thr Gly Arg Asp						
	610		615		620	
Tyr Thr Val Val Pro Ile Asp Asp Val Trp Asp Asp Ser Ile Met Leu						
	625		630		635	640
Ser Lys Asp Pro Ile Pro Pro Ile Val Gly Asn Ser Gly Asn Leu Ala						
	645		650		655	
Ile Ala Tyr Met Asp Val Phe Arg Pro Lys Val Pro Ile His Val Ala						
	660		665		670	

Met Thr Gly Ala Leu Asn Ala Cys Gly Glu Ile Glu Lys Val Ser Phe
 675 680 685

Arg Ser Thr Lys Leu Ala Thr Ala His Arg Leu Gly Leu Arg Leu Ala
 690 695 700

Gly Pro Gly Ala Phe Asp Val Asn Thr Gly Pro Asn Trp Ala Thr Phe
 705 710 715 720

Ile Lys Arg Phe Pro His Asn Pro Arg Asp Trp Asp Arg Leu Pro Tyr
 725 730 735

Leu Asn Leu Pro Tyr Leu Pro Pro Asn Ala Gly Arg Gln Tyr His Leu
 740 745 750

Ala Met Ala Ala Ser Glu Phe Lys Glu Thr Pro Glu Leu Glu Ser Ala
 755 760 765

Val Arg Ala Met Glu Ala Ala Ala Asn Val Asp Pro Leu Phe Gln Ser
 770 775 780

Ala Leu Ser Val Phe Met Trp Leu Glu Glu Asn Gly Ile Val Thr Asp
 785 790 795 800

Met Ala Asn Phe Ala Leu Ser Asp Pro Asn Ala His Arg Met Arg Asn
 805 810 815

Phe Leu Ala Asn Ala Pro Gln Ala Gly Ser Lys Ser Gln Arg Ala Lys
 820 825 830

Tyr Gly Thr Ala Gly Tyr Gly Val Glu Ala Arg Gly Pro Thr Pro Glu
 835 840 845

Glu Ala Gln Arg Glu Lys Asp Thr Arg Ile Ser Lys Lys Met Glu Thr
 850 855 860

Met Gly Ile Tyr Phe Ala Thr Pro Glu Trp Val Ala Leu Asn Gly His
 865 870 875 880

Arg Gly Pro Ser Pro Gly Gln Leu Lys Tyr Trp Gln Asn Thr Arg Glu
 885 890 895

Ile Pro Asp Pro Asn Glu Asp Tyr Leu Asp Tyr Val His Ala Glu Lys
 900 905 910

Ser Arg Leu Ala Ser Glu Glu Gln Ile Leu Arg Ala Ala Thr Ser Ile
 915 920 925

Tyr Gly Ala Pro Gly Gln Ala Glu Pro Pro Gln Ala Phe Ile Asp Glu
 930 935 940

Val Ala Lys Val Tyr Glu Ile Asn His Gly Arg Gly Pro Asn Gln Glu

[illegible]

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3264 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) **FEATURE:**

- (A) NAME/KEY: CDS
(B) LOCATION: 97..531

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GGATACGATC GGTCTGACCC CGGGGGAGTC ACCCGGGGAC AGGCCATCAC TGCCTTGTTT	60
CTGGTTGGAA CTCCTCTTTC TGCTGTACTA TCGTTG ATG GTG AGT AGA GAT CAG Met Val Ser Arg Asp Gln 1015	114
ACA AAC GAT CGC AGC GAT GAC AAA CCT GAT GGA TCA CAC CCA ACA GAT Thr Asn Asp Arg Ser Asp Asp Lys Pro Asp Gly Ser His Pro Thr Asp 1020 1025 1030	162
TGT TCC GTT CAT ACG GAG CCT TCT GAT GCC AAC GAC CGG ACC GGC GTC Cys Ser Val His Thr Glu Pro Ser Asp Ala Asn Asp Arg Thr Gly Val 1035 1040 1045 1050	210
CAT TCC GGA CGA CAC CCT GGA GAA GCA CAC ACT CAG GTC CGA AAC CTC His Ser Gly Arg His Pro Gly Glu Ala His Thr Gln Val Arg Asn Leu 1055 1060 1065	258
GAC TTA CAA CTT GAC TGT AGG GGA TAC AGG GTC AGG ACT AAT TGT CTT	306

Asp	Leu	Gln	Leu	Asp	Cys	Arg	Gly	Tyr	Arg	Val	Arg	Thr	Asn	Cys	Leu		
1070				1075				1080									
TTT	CCC	TGG	ATT	CCC	TGG	TTC	AGT	TGT	AGG	TGC	TCA	CTA	CAC	ACT	GCA	354	
Phe	Pro	Trp	Ile	Pro	Trp	Phe	Ser	Cys	Arg	Cys	Ser	Leu	His	Thr	Ala		
1085				1090				1095									
GAG	CAG	TGG	GAA	CTA	CCA	ATT	CGA	CCA	GAT	GCT	CCT	GAC	AGC	GCA	GAA	402	
Glu	Gln	Trp	Glu	Leu	Pro	Ile	Arg	Pro	Asp	Ala	Pro	Asp	Ser	Ala	Glu		
1100				1105				1110									
CCT	GCC	TGC	CAG	CTA	CAA	CTA	CTG	CAG	GCT	AGT	GAG	CAG	GAG	TCT	AAC	450	
Pro	Ala	Cys	Gln	Leu	Gln	Leu	Leu	Gln	Ala	Ser	Glu	Gln	Glu	Ser	Asn		
1115				1120				1125				1130					
CGT	ACG	GTC	AAG	CAC	ACT	CCC	TGG	TGG	CGT	TTA	TGC	ACT	AAA	CGG	AAC	498	
Arg	Thr	Val	Lys	His	Thr	Pro	Trp	Trp	Arg	Leu	Cys	Thr	Lys	Arg	Asn		
1135				1140				1145									
CAT	AAA	CGC	AGT	GAC	CTT	CCA	CGG	AAG	CCT	GAG	TGAGTTGACT	GACTACAGCT				551	
His	Lys	Arg	Ser	Asp	Leu	Pro	Arg	Lys	Pro	Glu							
1150				1155													
ACAACGGGCT	GATGTCAGCC	ACTGCGAACA	TCAACGACAA	GATCGGGAAC	GTCTAGTTG												611
GAGAAGGGGT	GACTGTTCTC	AGTCTACCGA	CTTCATATGA	CCTTAGTTAT	GTGAGACTCG												671
GTGACCCCAT	CCCCGCAGCA	GGACTCGACC	CGAAGTTGAT	GGCCACGTGC	GACAGTAGTG												731
ACAGACCCAG	AGTCTACACC	ATAACAGCTG	CAGATGAATA	CCAATTCTCG	TCACAACTCA												791
TCCCGAGTGG	CGTGAAGACC	ACACTGTTCT	CCGCCAACAT	CGATGCTCTC	ACCAGCTTCA												851
GCGTTGGTGG	TGAGCTTGTC	TTCAGCCAAG	TAACGATCCA	AAGCATTGAA	GTGGACGTCA												911
CCATTCACTT	CATTGGGTTT	GACGGGACAG	ACGTAGCAGT	CAAGGCAGTT	GCAACAGACT												971
TTGGGCTGAC	AACTGGGACA	AACAACCTTG	TGCCATTCAA	CCTGGTGGTC	CCAACAAATG												1031
AGATCACCCA	GCCCATCACT	TCCATGAAAC	TAGAGGTTGT	GACCTACAAG	ATTGGCGGCA												1091
CCGCTGGTGA	CCCAATATCA	TGGACAGTGA	GTGGTACACT	AGCTGTGACG	GTGCACGGAG												1151
GCAACTACCC	TGGGGCTCTC	CGTCCTGTCA	CCCTGGTGGC	CTATGAACGA	GTGGCTGCAG												1211
GATCTGTTGT	CACAGTTGCA	GGGGTGAGCA	ACTTCGAGCT	AATCCCCAAC	CCTGAGCTTG												1271
CAAAGAACCT	AGTTACAGAG	TATGGCCGCT	TTGACCCCGG	AGCAATGAAC	TACACCAAAC												1331
TAATACTGAG	TGAGAGAGAT	CGTCTAGGCA	TCAAGACAGT	CTGGCCCACC	AGGGAGTACA												1391
CCGATTTTCAG	GGAGTACTTC	ATGGAGGTTG	CAGATCTCAA	CTCACCCTTA	AAGATTGCAG												1451

GAGCATTGG	CTTTAAGGAC	ATAATCCGAG	CCATTCGGAA	GATTGCGGTG	CCAGTGGTAT	1511
CCACACTCTT	CCCTCCAGCT	GCACCCCTAG	CACATGCAAT	CGGAGAAGGT	GTAAGTACC	1571
TCCTGGGCGA	CGAGGCCCAA	GCAGCCTCAG	GGACAGCTCG	AGCCGCGTCA	GGAAAAGCTA	1631
GAGCTGCCTC	AGGACGAATA	AGGCAGCTAA	CTCTCGCAGC	TGACAAGGGG	TGCGAGGTAG	1691
TCGCCAACAT	GTTCCAGGTG	CCCCAGAATC	CCATTGTTGA	TGGCATTCTG	GCATCCCCAG	1751
GAATCCTGCG	TGGCGCACAC	AACCTCGACT	GCGTGCTATG	GGAGGGAGCC	ACTCTTTTCC	1811
CTGTTGTCAT	TACGACACTC	GAGGATGAGC	TGACCCCAA	GGCACTGAAC	AGCAAAATGT	1871
TTGCTGTCAT	TGAAGGTGTG	CGAGAGGACC	TCCAGCCTCC	ATCCCAACGG	GGATCCTTCA	1931
TTCGAACTCT	CTCTGGCCAT	AGAGTCTATG	GCTATGCCCC	AGACGGAGTA	CTGCCTCTGG	1991
AGACCGGGAG	AGACTACACC	GTTGTCCCAA	TTGATGATGT	GTGGGACGAT	AGCATAATGC	2051
TGTCGCAGGA	CCCATACCT	CCAATCATAG	GGAACAGCGG	CAACCTAGCC	ATAGCATACA	2111
TGGATGTCTT	CAGGCCCAAG	GTCCCCATCC	ACGTGGCTAT	GACAGGGGCC	CTCAATGCCC	2171
GCGGTGAGAT	CGAGAGTGTT	ACGTTCCGCA	GCACCAAAC	CGCCACAGCC	CACCGACTTG	2231
GCATGAAGTT	AGCTGGTCCT	GGAGCCTATG	ACATTAATAC	AGGACCTAAC	TGGGCAACGT	2291
TCGTCAAACG	TTTCCCTCAC	AATCCCCGAG	ACTGGGACAG	GTTGCCCTAC	CTCAACCTTC	2351
CTTATCTCCC	ACCAACAGCA	GGACGTCAGT	TCCATCTAGC	CCTGGCTGCC	TCCGAGTTCA	2411
AAGAGACCCC	AGAACTCGAA	GACGCTGTGC	GCGCAATGGA	TGCCGCTGCA	AATGCCGACC	2471
CATTGTTCCG	CTCAGCTCTC	CAGGTCTTCA	TGTGGTTGGA	AGAAAACGGG	ATTGTGACCG	2531
ACATGGCTAA	CTTCGCCCTC	AGCGACCCAA	ACGCGCATAG	GATGAAAAAC	TTCCTAGCAA	2591
ACGCACCCCA	GGCTGGAAGC	AAGTCGCAGA	GGGCAAGTA	TGGCACGGCA	GGCTACGGAG	2651
TGGAGGCTCG	AGGCCCCACA	CCAGAAGAGG	CACAGAGGGA	AAAAGACACA	CGGATCTCCA	2711
AGAAGATGGA	AACAATGGGC	ATCTACTTCG	CGACACCGGA	ATGGGTGGCT	CTCAACGGGC	2771
ACCGAGGCCC	AAGCCCCGGC	CAACTCAAGT	ACTGGCAAAA	CACAAGAGAA	ATACCAGAGC	2831
CCAATGAGGA	CTACCCAGAC	TATGTGCACG	CGGAGAAGAG	CCGGTTGGCG	TCAGAAGAAC	2891
AGATCCTACG	GGCAGCCACG	TCGATCTACG	GGGCTCCAGG	ACAGGCTGAA	CCACCCAGG	2951
CCTTCATAGA	CGAGGTCGCC	AGGGTCTATG	AAATCAACCA	TGGGCGTGGT	CCAAACCAGG	3011

AGCAGATGAA GGACCTGCTC CTGACTGCGA TGGAGATGAA GCATCGCAAT CCCAGGCGGG 3071
 CTCCACCAAA GCCAAAGCCA AAACCCAATG CTCCATCACA GAGACCCCCT GGACGGCTGG 3131
 GCCGCTGGAT CAGGACGGTC TCCGACGAGG ACTTGGAGTG AGGCTCCTGG GAGTCTCCCG 3191
 ACACTACCCG CGCAGGTGTG GACACCAATT CGGCCTTCTA CCATCCCAA TTGGATCCGT 3251
 TCGCGGGTCC CCT 3264

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 145 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Val Ser Arg Asp Gln Thr Asn Asp Arg Ser Asp Asp Lys Pro Asp
 1 5 10 15
 Gly Ser His Pro Thr Asp Cys Ser Val His Thr Glu Pro Ser Asp Ala
 20 25 30
 Asn Asp Arg Thr Gly Val His Ser Gly Arg His Pro Gly Glu Ala His
 35 40 45
 Thr Gln Val Arg Asn Leu Asp Leu Gln Leu Asp Cys Arg Gly Tyr Arg
 50 55 60
 Val Arg Thr Asn Cys Leu Phe Pro Trp Ile Pro Trp Phe Ser Cys Arg
 65 70 75 80
 Cys Ser Leu His Thr Ala Glu Gln Trp Glu Leu Pro Ile Arg Pro Asp
 85 90 95
 Ala Pro Asp Ser Ala Glu Pro Ala Cys Gln Leu Gln Leu Gln Ala
 100 105 110
 Ser Glu Gln Glu Ser Asn Arg Thr Val Lys His Thr Pro Trp Trp Arg
 115 120 125
 Leu Cys Thr Lys Arg Asn His Lys Arg Ser Asp Leu Pro Arg Lys Pro
 130 135 140
 Glu
 145

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3264 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) **FEATURE:**

- (A) NAME/KEY: CDS
(B) LOCATION: 131..3169

(xi) SEQUENCE DESCRIPTION: SEO ID NO:33:

GGATACGATC	GGTCTGACCC	CGGGGGAGTC	ACCCGGGGAC	AGGCCATCAC	TGCCTTGTTC		60
CTGGTTGGAA	CTCCTCTTTC	TGCTGTACTA	TCGTTGATGG	TGAGTAGAGA	TCAGACAAAC		120
GATCGCAGCG	ATG ACA AAC	CTG ATG GAT	CAC ACC CAA	CAG ATT GTT	CCG		169
	Met Thr Asn	Leu Met Asp	His Thr Gln	Ile Val Pro			
		150		155			
TTC ATA CGG	AGC CTT CTG	ATG CCA ACG	ACC GGA CCG	GCG TCC ATT	CCG		217
Phe Ile Arg	Ser Leu Leu	Met Pro Thr	Thr Gly Pro	Ala Ser Ile	Pro		
	160	165		170			
GAC GAC ACC	CTG GAG AAG	CAC ACA CTC	AGG TCC GAA	ACC TCG ACT	TAC		265
Asp Asp Thr	Leu Glu Lys	His Thr Leu	Arg Ser Glu	Thr Ser Thr	Tyr		
175		180		185	190		
AAC TTG ACT	GTA GGG GAT	ACA GGG TCA	GGA CTA ATT	GTC TTT TTC	CCT		313
Asn Leu Thr	Val Gly Asp	Thr Gly Ser	Gly Leu Ile	Val Phe Phe	Pro		
	195		200		205		
GGA TTC CCT	GGT TCA GTT	GTA GGT GCT	CAC TAC ACA	CTG CAG AGC	AGT		361
Gly Phe Pro	Gly Ser Val	Val Gly Ala	His Tyr Thr	Leu Gln Ser	Ser		
	210		215		220		
GGG AAC TAC	CAA TTC GAC	CAG ATG CTC	CTG ACA GCG	CAG AAC CTG	CCT		409
Gly Asn Tyr	Gln Phe Asp	Gln Met Leu	Leu Thr Ala	Gln Asn Leu	Pro		
	225		230		235		
GCC AGC TAC	AAC TAC TGC	AGG CTA GTG	AGC AGG AGT	CTA ACC GTA	CGG		457
Ala Ser Tyr	Asn Tyr Cys	Arg Leu Val	Ser Arg Ser	Leu Thr Val	Arg		
	240		245		250		

TCA	AGC	ACA	CTC	CCT	GGT	GGC	GTT	TAT	GCA	CTA	AAC	GGA	ACC	ATA	AAC	505
Ser	Ser	Thr	Leu	Pro	Gly	Gly	Val	Tyr	Ala	Leu	Asn	Gly	Thr	Ile	Asn	
255					260					265					270	
GCA	GTG	ACC	TTC	CAC	GGA	AGC	CTG	AGT	GAG	TTG	ACT	GAC	TAC	AGC	TAC	553
Ala	Val	Thr	Phe	His	Gly	Ser	Leu	Ser	Glu	Leu	Thr	Asp	Tyr	Ser	Tyr	
				275					280					285		
AAC	GGG	CTG	ATG	TCA	GCC	ACT	GCG	AAC	ATC	AAC	GAC	AAG	ATC	GGG	AAC	601
Asn	Gly	Leu	Met	Ser	Ala	Thr	Ala	Asn	Ile	Asn	Asp	Lys	Ile	Gly	Asn	
			290					295					300			
GTT	CTA	GTT	GGA	GAA	GGG	GTG	ACT	GTT	CTC	AGT	CTA	CCG	ACT	TCA	TAT	649
Val	Leu	Val	Gly	Glu	Gly	Val	Thr	Val	Leu	Ser	Leu	Pro	Thr	Ser	Tyr	
	305						310					315				
GAC	CTT	AGT	TAT	GTG	AGA	CTC	GGT	GAC	CCC	ATC	CCC	GCA	GCA	GGA	CTC	697
Asp	Leu	Ser	Tyr	Val	Arg	Leu	Gly	Asp	Pro	Ile	Pro	Ala	Ala	Gly	Leu	
	320					325					330					
GAC	CCG	AAG	TTG	ATG	GCC	ACG	TGC	GAC	AGT	AGT	GAC	AGA	CCC	AGA	GTC	745
Asp	Pro	Lys	Leu	Met	Ala	Thr	Cys	Asp	Ser	Ser	Asp	Arg	Pro	Arg	Val	
335					340					345					350	
TAC	ACC	ATA	ACA	GCT	GCA	GAT	GAA	TAC	CAA	TTC	TCG	TCA	CAA	CTC	ATC	793
Tyr	Thr	Ile	Thr	Ala	Ala	Asp	Glu	Tyr	Gln	Phe	Ser	Ser	Gln	Leu	Ile	
				355					360					365		
CCG	AGT	GGC	GTG	AAG	ACC	ACA	CTG	TTC	TCC	GCC	AAC	ATC	GAT	GCT	CTC	841
Pro	Ser	Gly	Val	Lys	Thr	Thr	Leu	Phe	Ser	Ala	Asn	Ile	Asp	Ala	Leu	
			370					375					380			
ACC	AGC	TTC	AGC	GTT	GGT	GGT	GAG	CTT	GTC	TTC	AGC	CAA	GTA	ACG	ATC	889
Thr	Ser	Phe	Ser	Val	Gly	Gly	Glu	Leu	Val	Phe	Ser	Gln	Val	Thr	Ile	
	385						390					395				
CAA	AGC	ATT	GAA	GTG	GAC	GTC	ACC	ATT	CAC	TTC	ATT	GGG	TTT	GAC	GGG	937
Gln	Ser	Ile	Glu	Val	Asp	Val	Thr	Ile	His	Phe	Ile	Gly	Phe	Asp	Gly	
	400					405					410					
ACA	GAC	GTA	GCA	GTC	AAG	GCA	GTT	GCA	ACA	GAC	TTT	GGG	CTG	ACA	ACT	985
Thr	Asp	Val	Ala	Val	Lys	Ala	Val	Ala	Thr	Asp	Phe	Gly	Leu	Thr	Thr	
415					420					425					430	
GGG	ACA	AAC	AAC	CTT	GTG	CCA	TTC	AAC	CTG	GTG	GTC	CCA	ACA	AAT	GAG	1033
Gly	Thr	Asn	Asn	Leu	Val	Pro	Phe	Asn	Leu	Val	Val	Pro	Thr	Asn	Glu	
				435					440					445		
ATC	ACC	CAG	CCC	ATC	ACT	TCC	ATG	AAA	CTA	GAG	GTT	GTG	ACC	TAC	AAG	1081
Ile	Thr	Gln	Pro	Ile	Thr	Ser	Met	Lys	Leu	Glu	Val	Val	Thr	Tyr	Lys	
			450					455					460			

ATT	GGC	GGC	ACC	GCT	GGT	GAC	CCA	ATA	TCA	TGG	ACA	GTG	AGT	GGT	ACA	1129
Ile	Gly	Gly	Thr	Ala	Gly	Asp	Pro	Ile	Ser	Trp	Thr	Val	Ser	Gly	Thr	
	465						470					475				
CTA	GCT	GTG	ACG	GTG	CAC	GGA	GGC	AAC	TAC	CCT	GGG	GCT	CTC	CGT	CCT	1177
Leu	Ala	Val	Thr	Val	His	Gly	Gly	Asn	Tyr	Pro	Gly	Ala	Leu	Arg	Pro	
	480					485					490					
GTC	ACC	CTG	GTG	GCC	TAT	GAA	CGA	GTG	GCT	GCA	GGA	TCT	GTT	GTC	ACA	1225
Val	Thr	Leu	Val	Ala	Tyr	Glu	Arg	Val	Ala	Ala	Gly	Ser	Val	Val	Thr	
495					500					505					510	
GTT	GCA	GGG	GTG	AGC	AAC	TTC	GAG	CTA	ATC	CCC	AAC	CCT	GAG	CTT	GCA	1273
Val	Ala	Gly	Val	Ser	Asn	Phe	Glu	Leu	Ile	Pro	Asn	Pro	Glu	Leu	Ala	
				515					520					525		
AAG	AAC	CTA	GTT	ACA	GAG	TAT	GGC	CGC	TTT	GAC	CCC	GGA	GCA	ATG	AAC	1321
Lys	Asn	Leu	Val	Thr	Glu	Tyr	Gly	Arg	Phe	Asp	Pro	Gly	Ala	Met	Asn	
		530						535					540			
TAC	ACC	AAA	CTA	ATA	CTG	AGT	GAG	AGA	GAT	CGT	CTA	GGC	ATC	AAG	ACA	1369
Tyr	Thr	Lys	Leu	Ile	Leu	Ser	Glu	Arg	Asp	Arg	Leu	Gly	Ile	Lys	Thr	
		545					550					555				
GTC	TGG	CCC	ACC	AGG	GAG	TAC	ACC	GAT	TTC	AGG	GAG	TAC	TTC	ATG	GAG	1417
Val	Trp	Pro	Thr	Arg	Glu	Tyr	Thr	Asp	Phe	Arg	Glu	Tyr	Phe	Met	Glu	
	560					565					570					
GTT	GCA	GAT	CTC	AAC	TCA	CCC	CTA	AAG	ATT	GCA	GGA	GCA	TTT	GGC	TTT	1465
Val	Ala	Asp	Leu	Asn	Ser	Pro	Leu	Lys	Ile	Ala	Gly	Ala	Phe	Gly	Phe	
575					580					585					590	
AAG	GAC	ATA	ATC	CGA	GCC	ATT	CGG	AAG	ATT	GCG	GTG	CCA	GTG	GTA	TCC	1513
Lys	Asp	Ile	Ile	Arg	Ala	Ile	Arg	Lys	Ile	Ala	Val	Pro	Val	Val	Ser	
				595					600					605		
ACA	CTC	TTC	CCT	CCA	GCT	GCA	CCC	CTA	GCA	CAT	GCA	ATC	GGA	GAA	GGT	1561
Thr	Leu	Phe	Pro	Pro	Ala	Ala	Pro	Leu	Ala	His	Ala	Ile	Gly	Glu	Gly	
			610					615					620			
GTA	GAC	TAC	CTC	CTG	GGC	GAC	GAG	GCC	CAA	GCA	GCC	TCA	GGG	ACA	GCT	1609
Val	Asp	Tyr	Leu	Leu	Gly	Asp	Glu	Ala	Gln	Ala	Ala	Ser	Gly	Thr	Ala	
		625					630					635				
CGA	GCC	GCG	TCA	GGA	AAA	GCT	AGA	GCT	GCC	TCA	GGA	CGA	ATA	AGG	CAG	1657
Arg	Ala	Ala	Ser	Gly	Lys	Ala	Arg	Ala	Ala	Ser	Gly	Arg	Ile	Arg	Gln	
	640					645					650					
CTA	ACT	CTC	GCA	GCT	GAC	AAG	GGG	TGC	GAG	GTA	GTC	GCC	AAC	ATG	TTC	1705
Leu	Thr	Leu	Ala	Ala	Asp	Lys	Gly	Cys	Glu	Val	Val	Ala	Asn	Met	Phe	
655					660					665					670	

CAG	GTG	CCC	CAG	AAT	CCC	ATT	GTT	GAT	GGC	ATT	CTG	GCA	TCC	CCA	GGA	1753
Gln	Val	Pro	Gln	Asn	Pro	Ile	Val	Asp	Gly	Ile	Leu	Ala	Ser	Pro	Gly	
				675					680						685	
ATC	CTG	CGT	GGC	GCA	CAC	AAC	CTC	GAC	TGC	GTG	CTA	TGG	GAG	GGA	GCC	1801
Ile	Leu	Arg	Gly	Ala	His	Asn	Leu	Asp	Cys	Val	Leu	Trp	Glu	Gly	Ala	
			690					695					700			
ACT	CTT	TTC	CCT	GTT	GTC	ATT	ACG	ACA	CTC	GAG	GAT	GAG	CTG	ACC	CCC	1849
Thr	Leu	Phe	Pro	Val	Val	Ile	Thr	Thr	Leu	Glu	Asp	Glu	Leu	Thr	Pro	
		705					710					715				
AAG	GCA	CTG	AAC	AGC	AAA	ATG	TTT	GCT	GTC	ATT	GAA	GGT	GTG	CGA	GAG	1897
Lys	Ala	Leu	Asn	Ser	Lys	Met	Phe	Ala	Val	Ile	Glu	Gly	Val	Arg	Glu	
	720					725					730					
GAC	CTC	CAG	CCT	CCA	TCC	CAA	CGG	GGA	TCC	TTC	ATT	CGA	ACT	CTC	TCT	1945
Asp	Leu	Gln	Pro	Pro	Ser	Gln	Arg	Gly	Ser	Phe	Ile	Arg	Thr	Leu	Ser	
	735					740					745				750	
GGC	CAT	AGA	GTC	TAT	GGC	TAT	GCC	CCA	GAC	GGA	GTA	CTG	CCT	CTG	GAG	1993
Gly	His	Arg	Val	Tyr	Gly	Tyr	Ala	Pro	Asp	Gly	Val	Leu	Pro	Leu	Glu	
				755					760					765		
ACC	GGG	AGA	GAC	TAC	ACC	GTT	GTC	CCA	ATT	GAT	GAT	GTG	TGG	GAC	GAT	2041
Thr	Gly	Arg	Asp	Tyr	Thr	Val	Val	Pro	Ile	Asp	Asp	Val	Trp	Asp	Asp	
			770					775					780			
AGC	ATA	ATG	CTG	TCG	CAG	GAC	CCC	ATA	CCT	CCA	ATC	ATA	GGG	AAC	AGC	2089
Ser	Ile	Met	Leu	Ser	Gln	Asp	Pro	Ile	Pro	Pro	Ile	Ile	Gly	Asn	Ser	
		785					790					795				
GGC	AAC	CTA	GCC	ATA	GCA	TAC	ATG	GAT	GTC	TTC	AGG	CCC	AAG	GTC	CCC	2137
Gly	Asn	Leu	Ala	Ile	Ala	Tyr	Met	Asp	Val	Phe	Arg	Pro	Lys	Val	Pro	
	800					805					810					
ATC	CAC	GTG	GCT	ATG	ACA	GGG	GCC	CTC	AAT	GCC	CGC	GGT	GAG	ATC	GAG	2185
Ile	His	Val	Ala	Met	Thr	Gly	Ala	Leu	Asn	Ala	Arg	Gly	Glu	Ile	Glu	
	815				820					825					830	
AGT	GTT	ACG	TTC	CGC	AGC	ACC	AAA	CTC	GCC	ACA	GCC	CAC	CGA	CTT	GGC	2233
Ser	Val	Thr	Phe	Arg	Ser	Thr	Lys	Leu	Ala	Thr	Ala	His	Arg	Leu	Gly	
				835					840					845		
ATG	AAG	TTA	GCT	GGT	CCT	GGA	GCC	TAT	GAC	ATT	AAT	ACA	GGA	CCT	AAC	2281
Met	Lys	Leu	Ala	Gly	Pro	Gly	Ala	Tyr	Asp	Ile	Asn	Thr	Gly	Pro	Asn	
			850					855					860			
TGG	GCA	ACG	TTC	GTC	AAA	CGT	TTC	CCT	CAC	AAT	CCC	CGA	GAC	TGG	GAC	2329
Trp	Ala	Thr	Phe	Val	Lys	Arg	Phe	Pro	His	Asn	Pro	Arg	Asp	Trp	Asp	
			865				870					875				

AGG	TTG	CCC	TAC	CTC	AAC	CTT	CCT	TAT	CTC	CCA	CCA	ACA	GCA	GGA	CGT	2377
Arg	Leu	Pro	Tyr	Leu	Asn	Leu	Pro	Tyr	Leu	Pro	Pro	Thr	Ala	Gly	Arg	
880					885					890						
CAG	TTC	CAT	CTA	GCC	CTG	GCT	GCC	TCC	GAG	TTC	AAA	GAG	ACC	CCA	GAA	2425
Gln	Phe	His	Leu	Ala	Leu	Ala	Ala	Ser	Glu	Phe	Lys	Glu	Thr	Pro	Glu	
895					900				905						910	
CTC	GAA	GAC	GCT	GTG	CGC	GCA	ATG	GAT	GCC	GCT	GCA	AAT	GCC	GAC	CCA	2473
Leu	Glu	Asp	Ala	Val	Arg	Ala	Met	Asp	Ala	Ala	Ala	Asn	Ala	Asp	Pro	
				915					920					925		
TTG	TTC	CGC	TCA	GCT	CTC	CAG	GTC	TTC	ATG	TGG	TTG	GAA	GAA	AAC	GGG	2521
Leu	Phe	Arg	Ser	Ala	Leu	Gln	Val	Phe	Met	Trp	Leu	Glu	Glu	Asn	Gly	
			930						935					940		
ATT	GTG	ACC	GAC	ATG	GCT	AAC	TTC	GCC	CTC	AGC	GAC	CCA	AAC	GCG	CAT	2569
Ile	Val	Thr	Asp	Met	Ala	Asn	Phe	Ala	Leu	Ser	Asp	Pro	Asn	Ala	His	
			945						950					955		
AGG	ATG	AAA	AAC	TTC	CTA	GCA	AAC	GCA	CCC	CAG	GCT	GGA	AGC	AAG	TCG	2617
Arg	Met	Lys	Asn	Phe	Leu	Ala	Asn	Ala	Pro	Gln	Ala	Gly	Ser	Lys	Ser	
960						965						970				
CAG	AGG	GCC	AAG	TAT	GGC	ACG	GCA	GGC	TAC	GGA	GTG	GAG	GCT	CGA	GGC	2665
Gln	Arg	Ala	Lys	Tyr	Gly	Thr	Ala	Gly	Tyr	Gly	Val	Glu	Ala	Arg	Gly	
975					980					985					990	
CCC	ACA	CCA	GAA	GAG	GCA	CAG	AGG	GAA	AAA	GAC	ACA	CGG	ATC	TCC	AAG	2713
Pro	Thr	Pro	Glu	Glu	Ala	Gln	Arg	Glu	Lys	Asp	Thr	Arg	Ile	Ser	Lys	
				995						1000					1005	
AAG	ATG	GAA	ACA	ATG	GGC	ATC	TAC	TTC	GCG	ACA	CCG	GAA	TGG	GTG	GCT	2761
Lys	Met	Glu	Thr	Met	Gly	Ile	Tyr	Phe	Ala	Thr	Pro	Glu	Trp	Val	Ala	
				1010					1015					1020		
CTC	AAC	GGG	CAC	CGA	GGC	CCA	AGC	CCC	GGC	CAA	CTC	AAG	TAC	TGG	CAA	2809
Leu	Asn	Gly	His	Arg	Gly	Pro	Ser	Pro	Gly	Gln	Leu	Lys	Tyr	Trp	Gln	
				1025					1030					1035		
AAC	ACA	AGA	GAA	ATA	CCA	GAG	CCC	AAT	GAG	GAC	TAC	CCA	GAC	TAT	GTG	2857
Asn	Thr	Arg	Glu	Ile	Pro	Glu	Pro	Asn	Glu	Asp	Tyr	Pro	Asp	Tyr	Val	
1040						1045					1050					
CAC	GCG	GAG	AAG	AGC	CGG	TTG	GCG	TCA	GAA	GAA	CAG	ATC	CTA	CGG	GCA	2905
His	Ala	Glu	Lys	Ser	Arg	Leu	Ala	Ser	Glu	Glu	Gln	Ile	Leu	Arg	Ala	
1055					1060					1065					1070	
GCC	ACG	TCG	ATC	TAC	GGG	GCT	CCA	GGA	CAG	GCT	GAA	CCA	CCC	CAG	GCC	2953
Ala	Thr	Ser	Ile	Tyr	Gly	Ala	Pro	Gly	Gln	Ala	Glu	Pro	Pro	Gln	Ala	
				1075					1080						1085	

TTC ATA GAC GAG GTC GCC AGG GTC TAT GAA ATC AAC CAT GGG CGT GGT 3001
 Phe Ile Asp Glu Val Ala Arg Val Tyr Glu Ile Asn His Gly Arg Gly
 1090 1095 1100

CCA AAC CAG GAG CAG ATG AAG GAC CTG CTC CTG ACT GCG ATG GAG ATG 3049
 Pro Asn Gln Glu Gln Met Lys Asp Leu Leu Leu Thr Ala Met Glu Met
 1105 1110 1115

AAG CAT CGC AAT CCC AGG CGG GCT CCA CCA AAG CCA AAG CCA AAA CCC 3097
 Lys His Arg Asn Pro Arg Arg Ala Pro Pro Lys Pro Lys Pro Lys Pro
 1120 1125 1130

AAT GCT CCA TCA CAG AGA CCC CCT GGA CGG CTG GGC CGC TGG ATC AGG 3145
 Asn Ala Pro Ser Gln Arg Pro Pro Gly Arg Leu Gly Arg Trp Ile Arg
 1135 1140 1145 1150

ACG GTC TCC GAC GAG GAC TTG GAG TGAGGCTCCT GGGAGTCTCC CGACACTACC 3199
 Thr Val Ser Asp Glu Asp Leu Glu
 1155

CGCGCAGGTG TGGACACCAA TTCGGCCTTC TACCATCCCA AATTGGATCC GTTCGCGGGT 3259
 CCCCT 3264

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1013 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Thr Asn Leu Met Asp His Thr Gln Gln Ile Val Pro Phe Ile Arg
 1 5 10 15

Ser Leu Leu Met Pro Thr Thr Gly Pro Ala Ser Ile Pro Asp Asp Thr
 20 25 30

Leu Glu Lys His Thr Leu Arg Ser Glu Thr Ser Thr Tyr Asn Leu Thr
 35 40 45

Val Gly Asp Thr Gly Ser Gly Leu Ile Val Phe Phe Pro Gly Phe Pro
 50 55 60

Gly Ser Val Val Gly Ala His Tyr Thr Leu Gln Ser Ser Gly Asn Tyr
 65 70 75 80

Gln Phe Asp Gln Met Leu Leu Thr Ala Gln Asn Leu Pro Ala Ser Tyr

60

					85						90					95
Asn	Tyr	Cys	Arg	Leu	Val	Ser	Arg	Ser	Leu	Thr	Val	Arg	Ser	Ser	Thr	
			100					105					110			
Leu	Pro	Gly	Gly	Val	Tyr	Ala	Leu	Asn	Gly	Thr	Ile	Asn	Ala	Val	Thr	
		115					120					125				
Phe	His	Gly	Ser	Leu	Ser	Glu	Leu	Thr	Asp	Tyr	Ser	Tyr	Asn	Gly	Leu	
	130					135					140					
Met	Ser	Ala	Thr	Ala	Asn	Ile	Asn	Asp	Lys	Ile	Gly	Asn	Val	Leu	Val	
145					150					155				160		
Gly	Glu	Gly	Val	Thr	Val	Leu	Ser	Leu	Pro	Thr	Ser	Tyr	Asp	Leu	Ser	
			165						170					175		
Tyr	Val	Arg	Leu	Gly	Asp	Pro	Ile	Pro	Ala	Ala	Gly	Leu	Asp	Pro	Lys	
			180					185					190			
Leu	Met	Ala	Thr	Cys	Asp	Ser	Ser	Asp	Arg	Pro	Arg	Val	Tyr	Thr	Ile	
		195					200					205				
Thr	Ala	Ala	Asp	Glu	Tyr	Gln	Phe	Ser	Ser	Gln	Leu	Ile	Pro	Ser	Gly	
	210					215					220					
Val	Lys	Thr	Thr	Leu	Phe	Ser	Ala	Asn	Ile	Asp	Ala	Leu	Thr	Ser	Phe	
225					230					235					240	
Ser	Val	Gly	Gly	Glu	Leu	Val	Phe	Ser	Gln	Val	Thr	Ile	Gln	Ser	Ile	
				245					250					255		
Glu	Val	Asp	Val	Thr	Ile	His	Phe	Ile	Gly	Phe	Asp	Gly	Thr	Asp	Val	
			260					265					270			
Ala	Val	Lys	Ala	Val	Ala	Thr	Asp	Phe	Gly	Leu	Thr	Thr	Gly	Thr	Asn	
		275					280						285			
Asn	Leu	Val	Pro	Phe	Asn	Leu	Val	Val	Pro	Thr	Asn	Glu	Ile	Thr	Gln	
	290					295					300					
Pro	Ile	Thr	Ser	Met	Lys	Leu	Glu	Val	Val	Thr	Tyr	Lys	Ile	Gly	Gly	
305					310					315					320	
Thr	Ala	Gly	Asp	Pro	Ile	Ser	Trp	Thr	Val	Ser	Gly	Thr	Leu	Ala	Val	
				325					330					335		
Thr	Val	His	Gly	Gly	Asn	Tyr	Pro	Gly	Ala	Leu	Arg	Pro	Val	Thr	Leu	
			340					345					350			
Val	Ala	Tyr	Glu	Arg	Val	Ala	Ala	Gly	Ser	Val	Val	Thr	Val	Ala	Gly	
		355					360						365			

Val	Ser	Asn	Phe	Glu	Leu	Ile	Pro	Asn	Pro	Glu	Leu	Ala	Lys	Asn	Leu	370	375	380	
Val	Thr	Glu	Tyr	Gly	Arg	Phe	Asp	Pro	Gly	Ala	Met	Asn	Tyr	Thr	Lys	385	390	395	400
Leu	Ile	Leu	Ser	Glu	Arg	Asp	Arg	Leu	Gly	Ile	Lys	Thr	Val	Trp	Pro	405	410	415	
Thr	Arg	Glu	Tyr	Thr	Asp	Phe	Arg	Glu	Tyr	Phe	Met	Glu	Val	Ala	Asp	420	425	430	
Leu	Asn	Ser	Pro	Leu	Lys	Ile	Ala	Gly	Ala	Phe	Gly	Phe	Lys	Asp	Ile	435	440	445	
Ile	Arg	Ala	Ile	Arg	Lys	Ile	Ala	Val	Pro	Val	Val	Ser	Thr	Leu	Phe	450	455	460	
Pro	Pro	Ala	Ala	Pro	Leu	Ala	His	Ala	Ile	Gly	Glu	Gly	Val	Asp	Tyr	465	470	475	480
Leu	Leu	Gly	Asp	Glu	Ala	Gln	Ala	Ala	Ser	Gly	Thr	Ala	Arg	Ala	Ala	485	490	495	
Ser	Gly	Lys	Ala	Arg	Ala	Ala	Ser	Gly	Arg	Ile	Arg	Gln	Leu	Thr	Leu	500	505	510	
Ala	Ala	Asp	Lys	Gly	Cys	Glu	Val	Val	Ala	Asn	Met	Phe	Gln	Val	Pro	515	520	525	
Gln	Asn	Pro	Ile	Val	Asp	Gly	Ile	Leu	Ala	Ser	Pro	Gly	Ile	Leu	Arg	530	535	540	
Gly	Ala	His	Asn	Leu	Asp	Cys	Val	Leu	Trp	Glu	Gly	Ala	Thr	Leu	Phe	545	550	555	560
Pro	Val	Val	Ile	Thr	Thr	Leu	Glu	Asp	Glu	Leu	Thr	Pro	Lys	Ala	Leu	565	570	575	
Asn	Ser	Lys	Met	Phe	Ala	Val	Ile	Glu	Gly	Val	Arg	Glu	Asp	Leu	Gln	580	585	590	
Pro	Pro	Ser	Gln	Arg	Gly	Ser	Phe	Ile	Arg	Thr	Leu	Ser	Gly	His	Arg	595	600	605	
Val	Tyr	Gly	Tyr	Ala	Pro	Asp	Gly	Val	Leu	Pro	Leu	Glu	Thr	Gly	Arg	610	615	620	
Asp	Tyr	Thr	Val	Val	Pro	Ile	Asp	Asp	Val	Trp	Asp	Asp	Ser	Ile	Met	625	630	635	640

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Leu Ser Gln Asp Pro Ile Pro Pro Ile Ile Gly Asn Ser Gly Asn Leu
 645 650 655
 Ala Ile Ala Tyr Met Asp Val Phe Arg Pro Lys Val Pro Ile His Val
 660 665 670
 Ala Met Thr Gly Ala Leu Asn Ala Arg Gly Glu Ile Glu Ser Val Thr
 675 680 685
 Phe Arg Ser Thr Lys Leu Ala Thr Ala His Arg Leu Gly Met Lys Leu
 690 695 700
 Ala Gly Pro Gly Ala Tyr Asp Ile Asn Thr Gly Pro Asn Trp Ala Thr
 705 710 715 720
 Phe Val Lys Arg Phe Pro His Asn Pro Arg Asp Trp Asp Arg Leu Pro
 725 730 735
 Tyr Leu Asn Leu Pro Tyr Leu Pro Pro Thr Ala Gly Arg Gln Phe His
 740 745 750
 Leu Ala Leu Ala Ala Ser Glu Phe Lys Glu Thr Pro Glu Leu Glu Asp
 755 760 765
 Ala Val Arg Ala Met Asp Ala Ala Ala Asn Ala Asp Pro Leu Phe Arg
 770 775 780
 Ser Ala Leu Gln Val Phe Met Trp Leu Glu Glu Asn Gly Ile Val Thr
 785 790 795 800
 Asp Met Ala Asn Phe Ala Leu Ser Asp Pro Asn Ala His Arg Met Lys
 805 810 815
 Asn Phe Leu Ala Asn Ala Pro Gln Ala Gly Ser Lys Ser Gln Arg Ala
 820 825 830
 Lys Tyr Gly Thr Ala Gly Tyr Gly Val Glu Ala Arg Gly Pro Thr Pro
 835 840 845
 Glu Glu Ala Gln Arg Glu Lys Asp Thr Arg Ile Ser Lys Lys Met Glu
 850 855 860
 Thr Met Gly Ile Tyr Phe Ala Thr Pro Glu Trp Val Ala Leu Asn Gly
 865 870 875 880
 His Arg Gly Pro Ser Pro Gly Gln Leu Lys Tyr Trp Gln Asn Thr Arg
 885 890 895
 Glu Ile Pro Glu Pro Asn Glu Asp Tyr Pro Asp Tyr Val His Ala Glu
 900 905 910

Lys Ser Arg Leu Ala Ser Glu Glu Gln Ile Leu Arg Ala Ala Thr Ser
915 920 925

Ile Tyr Gly Ala Pro Gly Gln Ala Glu Pro Pro Gln Ala Phe Ile Asp
930 935 940

Glu Val Ala Arg Val Tyr Glu Ile Asn His Gly Arg Gly Pro Asn Gln
945 950 955 960

Glu Gln Met Lys Asp Leu Leu Leu Thr Ala Met Glu Met Lys His Arg
965 970 975

Asn Pro Arg Arg Ala Pro Pro Lys Pro Lys Pro Lys Pro Asn Ala Pro
980 985 990

Ser Gln Arg Pro Pro Gly Arg Leu Gly Arg Trp Ile Arg Thr Val Ser
995 1000 1005

Asp Glu Asp Leu Glu
1010

Claims

1. A method for preparing live Birnavirus, comprising the following steps:
 - preparing a cDNA containing infectious bursal disease virus genome segments A and B,
 - transcribing said cDNA to produce synthetic RNA transcripts,
 - transfecting host cells with said synthetic RNA transcripts,
 - incubating said host cells in a culture medium, and
 - isolating live infectious bursal disease virus from said culture medium.
2. The method according to claim 1, wherein said Birnavirus is infectious bursal disease virus.
3. The method according to claim 1, wherein said host cells are African green monkey Vero cells.
4. The method according to claim 1, wherein said segments A and B of said cDNA are independently prepared.
5. The method according to claim 4, wherein said segment A is present in plasmid pUC19FLAD78 or pUC18FLA23.
6. The method according to claim 4, wherein said segment B is present in plasmid pUC18FLBP2.
7. A live infectious bursal disease virus, wherein said virus is made by a process comprising the steps of preparing a cDNA containing infectious bursal disease virus genome segments A and B,
 - transcribing said cDNA to produce a synthetic RNA transcript,
 - transfecting a host cell with said synthetic RNA transcript,
 - incubating said host cell in a culture medium, and
 - isolating live infectious bursal disease virus from said culture medium.
8. A synthetic RNA encoding proteins VP1, VP2, VP3, VP4, and VP5 of infectious bursal disease virus.
9. A host cell transfected with the synthetic RNA according to claim 8.
10. A cDNA containing at least a portion of the infectious bursal disease virus genome selected from the group consisting of segment A,

segment B and segments A and B of infectious bursal disease virus, wherein said cDNA includes the 5' and 3' termini of said segments.

11. A recombinant vector comprising the cDNA according to claim 10.

12. The vector according to claim 11, wherein said vector is a plasmid.

13. The vector according to claim 12, wherein said plasmid is selected from the group consisting of pUC19FLAD78, pUC18FLA23 and pUC19FLBP2.

14. A host cell transformed with the vector according to claim 11.

15. A vaccine comprising an infectious bursal disease virus according to claim 7, wherein said infectious bursal disease virus is inactivated or attenuated prior to administration.

16. A method for producing a live infectious bursal disease virus vaccine, comprising the steps of

preparing a full-length cDNA containing infectious bursal disease virus genome segments A and B,

transcribing said cDNA to produce synthetic RNA transcripts,

purifying said synthetic RNA transcripts,

transfecting host cells with said purified RNA transcripts,

incubating said host cells in a culture medium,

isolating live infectious bursal disease virus from said culture medium,

attenuating said live infectious bursal disease virus to produce a virus with reduced virulence, and

combining said live infectious bursal disease virus with a pharmaceutically acceptable carrier to produce a live infectious bursal disease virus vaccine.

17. The method according to claim 16, wherein said live infectious bursal disease virus is attenuated by serial passage or site directed mutagenesis.

18. The method according to claim 1, wherein said host cells are poultry cells.

19. The method according to claim 18, wherein said poultry cells are chicken, turkey, or quail cells.

20. The method according to claim 19, wherein said poultry cells are chicken embryo fibroblast cells or chicken embryo kidney cells.

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Fig. 1

Fig. 1A
Fig. 1B
Fig. 1C

Fig. 4

Fig. 4A
Fig. 4B

Fig. 5

Fig. 5A
Fig. 5B

Fig. 6

Fig. 6A
Fig. 6B

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segment A of
strain D78

pUC19FLAD78

SEQ ID No. 1

GAATTCGGCTTAAATACGACTCACTATAGGATACGATCGGTCTGAC
CTTAAGCCGAAATTATGCTGAGTGATATCCTATGCTAGCCAGACTG

EcoR I

SEQ ID No. 2

AATTGGATCCGTTCCGCGGTTCCCTGTACAAAGCCGAATTC
TTAACCTAGGCAAGCAGCCGACATGTTTCGCTTAAG

BstG I

EcoR I

Transcription →

Fig.1A

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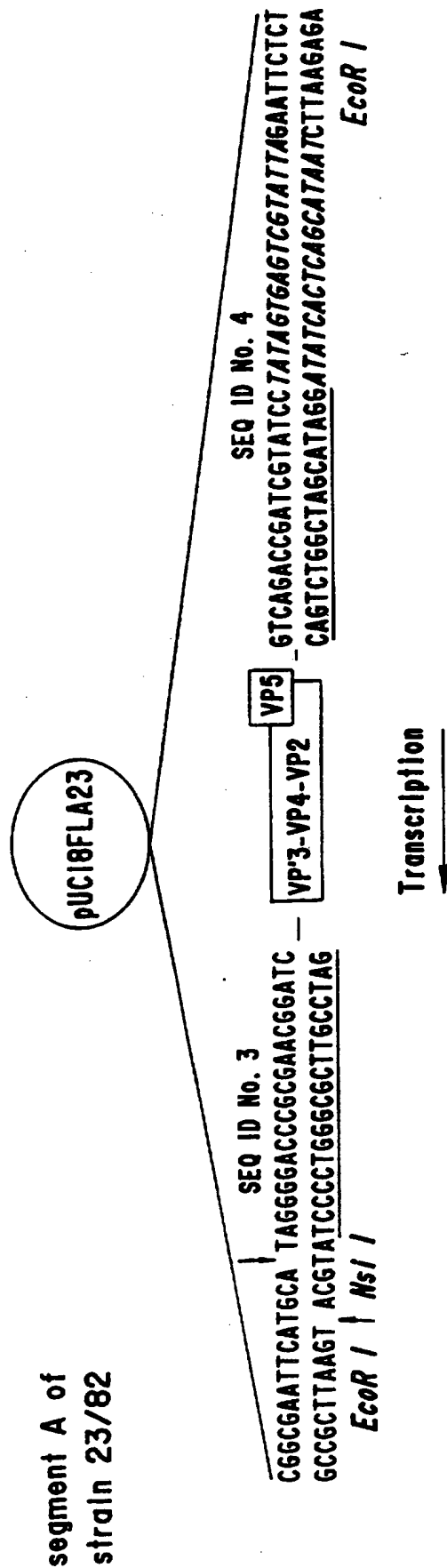


Fig.1B

pUC18FLBP2

of

↓ SEQ ID No. 5 ↓

TTGCAT6CCTGCA 66666CCCCC6CA6GGC6AA6 -

AACGTACGG ACGTCCCCC66666CGTCC6CTTC

↓ Pst I ↓

↓ SEQ ID No. 6 ↓

TCGTATCC7A7AGTG6AGTCG7ATT7AGAATTC

- VPI - AGCATAGGA7ATCACTCA6CATAA7CTTAAG

EcoR I

Transcription →

Fig. 1C

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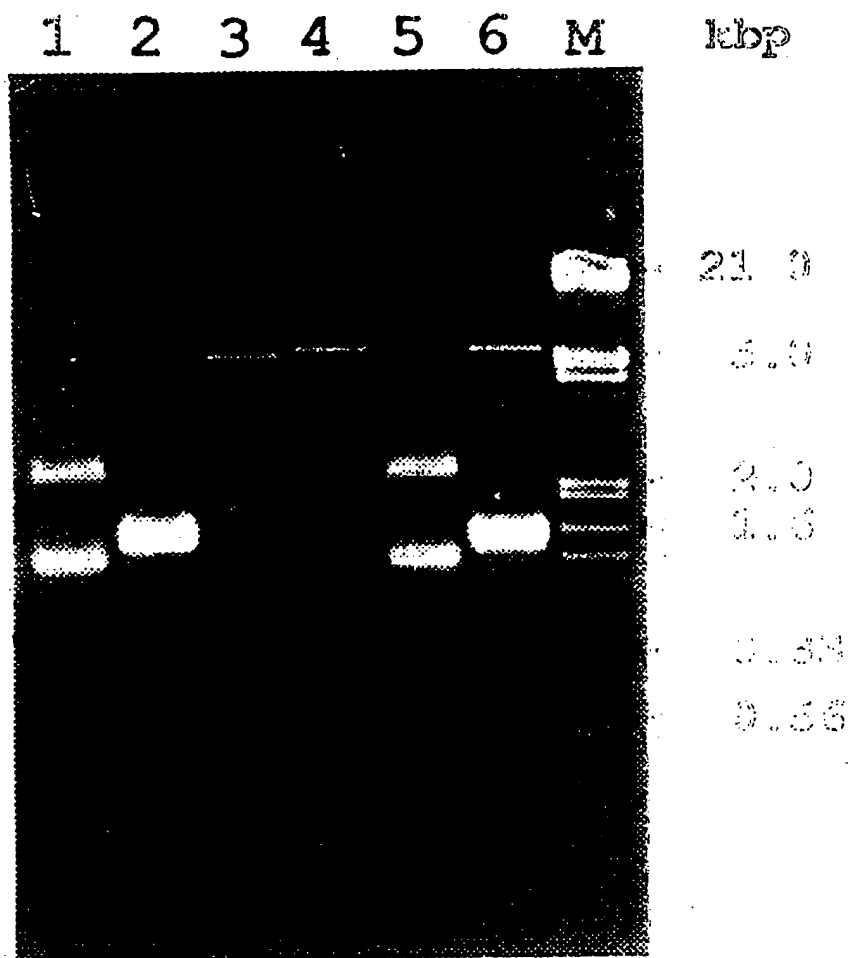


Fig. 2

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Segment A

23-82A
SEQ ID No. 723A/P2B
SEQ ID No. 8P2A
SEQ ID No. 9

530	540	550	560	570	580
66AAGCCTGAGTGAGTTGACTGACTACAGCTACAACGGGCTGATGTCAGCCACTGCCGAAC					
.....					
66AAGCCTGAGTGAGTTGACTGACTACAGCTACAACGGGCTGATGTCAGCCACTGCCGAAC					
.....					
66AAGCCTGAGTGAGTTGACTGACTACAGCTACAACGGGCTGATGTCAGCCACTGCCGAAC					
.....					
530	540	550	560	570	580
ATCAACGACAAAGATCGGGAAACGTTCTAGTTGGAGAAGGGGTGACTGTTCTCAGTCTACCG					
.....					
ATCAACGACAAAGATCGGGAAACGTTCTAGTTGGAGAAGGGGTGACTGTTCTCAGTCTACCG					
.....					
ATCAACGACAAAGATCGGGAAACGTTCTAGTTGGAGAAGGGGTGACTGTTCTCAGTCTACCG					
.....					
590	600	610	620	630	640
ATCAACGACAAAGATCGGGAAACGTTCTAGTTGGAGAAGGGGTGACTGTTCTCAGTCTACCG					
.....					
ATCAACGACAAAGATCGGGAAACGTTCTAGTTGGAGAAGGGGTGACTGTTCTCAGTCTACCG					
.....					
590	600	610	620	630	640

Fig.3A

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Segment B

23-82B	130	140	150	160	170	180
SEQ ID No. 10	TTTTCAATAGTCCACAGGCGGACGAAAGATCTCAGCAGCGTTTCGGCATAAAGCCTACTG					
23A/P2B	TTTTCAACAGTCCACAGGCGGACGAAAGATCTCAGCAGCGTTTCGGCATAAAGCCTACTG					
SEQ ID No. 11	TTTTCAACAGTCCACAGGCGGACGAAAGATCTCAGCAGCGTTTCGGCATAAAGCCTACTG					
P2B	TTTTCAACAGTCCACAGGCGGACGAAAGATCTCAGCAGCGTTTCGGCATAAAGCCTACTG					
SEQ ID No. 12	130	140	150	160	170	180
23-82B	190	200	210	220	230	240
SEQ ID No. 10	CTGGACAAGACGTGGAAAGAACTCTTGTATCCCCAAAGTCTG66T6CCACCTGAGGATCCGC					
23A/P2B	CTGGACAAGACGTGGAAAGAACTCTTGTATCCCCAAAGTCTG66T6CCACCTGAGGATCCGC					
SEQ ID No. 11	CTGGACAAGACGTGGAAAGAACTCTTGTATCCCCAAAGTCTG66T6CCACCTGAGGATCCGC					
P2B	CTGGACAAGACGTGGAAAGAACTCTTGTATCCCCAAAGTCTG66T6CCACCTGAGGATCCGC					
SEQ ID No. 12	190	200	210	220	230	240

Fig.3B

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Fig.4A

1 GGATACGATCGGTCTGACCCCGGGGAGTCAACCCGGGACAGGCCATCAGTGCCTTGTTCCTGGTTGGAA
 71 CTCCCTCTTCTGCTGTAATACTGTTGATGGTGGTAGAGATCAGACAAACGATCGCAGCGATGACAAACC
 141 TGATGGATCACACCCCAACAGATTGTTCCGTTTCATACGGAGCCTTCCTGATGCCAACGACCGGACCGCGTC
 211 CATTCCGGACGACACCTGGAGAAGCACACACTCAGGTCCGAACCTCGACTTACAACCTGACTGTAGGG
 281 GATACAGGGTCAGGACTAATTGCTTTTTCCCTGGATTCCTGGTTCAGTTGTAGGTGCTCACTACACAC
 351 TGCAGAGCAGTGGGAACACCAATTCGACCAGATGCTCTGACAGCGCAGAACCTGCCAGCTACAA
 421 CTACTGCAGGCTAGTGAGCAGGAGTCAACCGTACGGTCAAGCACACTCCCTGGTGGCGTTTATGCACATA
 491 AACGGAACCATAAACGCAGTGACCTTCCACGGAAGCCTGAGTGAGTTGACTGACTACAGCTACAACGGGC
 561 TGATGTCAGCCACTGCGAACAATCAACGACAAGATCGGGAACGTTCTAGTTGGAGAAGGGTGACTGTTCT
 631 CAGTCTACCGACTTCATATGACCTTAGTTATGTGAGACTCGGTGACCCCATCCCGCAGCAGGACTCGAC
 701 CCGAAGTTGATGGCCACGTGGACAGTAGTGACAGACCCAGAGTCTACACCATAAACAGCTGCAGATGAAT
 771 ACCAATTCTCGTCACAACTCATCCCGAGTGGCGTGAAGACCACACTGTTCTCCGCCAACATCGATGCTCT
 841 CACCAGCTTCAGCGTTGGTGGTGGCTTGTCTTCAGCCAAAGTAACGATCCAAAGCATTTGAAGTGGACGTC
 911 ACCATTCACTTCAATTGGGTTTGACGGGACAGACGTAGCAGTCAAGGCAGTTGCAACAGACTTTGGGCTGA
 981 CAACTGGGACAAACAACCTTGTGCCATTCAACCTGGTGGTCCCAACAATGAGATCACCCAGCCCATCAC
 1051 TTCCATGAAACTAGAGGTTGTGACCTACAAGATTGGCGGCACCGCTGGTGACCCAAATATCATGGACAGTG
 1121 AGTGGTACACTAGCTGTGACGGTGACGGAGGCAACTACCTGGGGCTCTCCGTCTGTCAACCTGGTGG
 1191 CCTATGAACGAGTGGCTGCAGGATCTGTTGTACAGTTGCAGGGGTGAGCAACTTCGAGCTAATCCCCAA
 1261 CCCTGAGCTTGCAAGAACCCTAGTTACAGAGTATGGCCGCTTGACCCCGGAGCAATGAACATACACCAA
 1331 CTAATACTGAGTGAGAGAGATCGTCTAGGCATCAAGACAGTCTGGCCCAACGAGGAGTACACCGATTGA
 1401 GGGAGTACTTCAATGGAGGTGCAGATCTCAACTCACCCCTAAAGATTGCAGGAGCATTTGGCTTTAAGGA
 1471 CATAATCCGAGGCCATTCCGAAGATTGCGGTGCCAGTGGTATCCACACTCTTCCCTCCAGCTGCACCCCTA
 1541 GCACATGCAATCGGAGAAGGTGTAGACTACCTCTGGGCGACGAGGCCCAAGCAGCTCAGGGACAGCTC
 1611 GAGCCGCTCAGGAAAGCTAGAGCTGCCTCAGGACGAATAAGGCAGCTAACTCTCGCAGCTGACAAGGG
 1681 GTGCGAGGTAGTCGCCAACATGTTCCAGGTGCCCCAGAAATCCCAATTGTTGATGGCATTTCTGGCATCCCCA
 1751 GGAATCCTGCGTGGCGCACACAACCTCGACTGCGTGCTATGGGAGGGAGGCCACTCTTTCCCTGTTGTCA

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1821 TTACGACACTCGAGGATGAGCTGACCCCCAAGGCACCTGAACAGCAAAATGTTGCTGTCATTGAAGGTGT
 1891 GCGAGAGGACCTCCAGCCTCCATCCCAACGGGGATCCTTCATTGGAACCTCTCTGGCCATAGAGTCTAT
 1961 GGCTATGCCCCAGACGGAGTACTGCTCTGGAGACCGGGAGAGACTACACCGTTGTCCCAATTGATGATG
 2031 TGTGGACGATAGCATAAATGCTGTGCGAGGACCCCATACCTCCAATCATAGGGAACAGCGCAACCTAGC
 2101 CATAGCATACATGGATGTCTTCAGGCCCAAGGTCCCCATCCACGTGGCTATGACAGGGGCCCTCAATGCC
 2171 CGCGGTGAGATCGAGAGTGTACGTTCCGVAGCACCAAACTCGCCACAGCCACCGACTTGGCATGAAGT
 2241 TAGCTGGTCTTGAGCCTATGACATTAAACAGGACCTAACTGGCAACGTTTCGTCAAACGTTTCCCTCA
 2311 CAATCCCCGAGACTGGGACAGGTGGCCCTACCTCAACCTTCCTTATCTCCACCAACAGCAGGACGTCAG
 2381 TTCCATCTAGCCCTGGCTGCCCTCCGAGTTCAAAGAGACCCAGAACTCGAAGACGCTGTGCGCGCAATGG
 2451 ATGCGGCTGCAATGCCGACCCATTGTTCCGCTCAGCTCTCCAGGTCTTCATGTGGTTGGAAGAAAACGG
 2521 GATTGTGACCGACATGGCTAACTTCGCCCTCAGCGACCCAAACGGGCATAGGATGAAAACCTTCCTAGCA
 2591 AAGCACCCCGAGGCTGGAAGCAAGTCGAGAGGGCCCAAGTATGGCACGGCAGGCTACGGAGTGGAGGCTC
 2661 GAGGCCCCACACACAGAAGAGGACAGAGGGAAGAACACACACGATCTCCAAGAAGATGGAACAAATGGG
 2731 CATCTACTTCGGGACACCGGAATGGGTGGCTCTCAACGGGCACCGAGGCCCAAGCCCGGCCAACTCAAG
 2801 TACTGGCAAAACACAGAGAAATACCAGAGCCCAATGAGGACTACCCAGACTATGTGCACGCGGAGAAGA
 2871 GCCGTTGGCGTCAGAAGAACAGATCCTACGGGCAGCCACGTCGATCTACGGGGCTCCAGGACAGGCTGA
 2941 ACCACCCCAAGCCTTCATAGACGAGGTGCGCCAGGGTCTATGAAATCAACCATGGGCGTGGTCCAACCCAG
 3011 GAGCAGATGAAGGACCTGCTCCTGACTGCGATGGAGATGAAGCATCGCAATCCCAGGCGGGCTCCACCAA
 3081 AGCCAAAGCCAAACCCCAATGCTCCATCACAGAGACCCCTGGACGGCTGGCCCGCTGGATCAGGACGGT
 3151 CTCCGACGAGGACTTGGAGTGAAGTCTCTGGAGTCTCCCGACACTACCCGCGCAGGTGTGGACACCAAT
 3221 TCGGCCCTTCTACCATCCCAATGGATCCGTTCCGCGGTCCCCCT

Total number of bases is: 3264.

DNA sequence composition: 834 A; 942 C; 853 G; 635 T;

Sequence name: 23-82A (SEQ ID NOS: 31 and 33)

Fig.4B

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Fig.5A

1	GGATACGATCGGTCGTGACCCCGGGGAGTCACCCGGGGACAGGCCGTCAGGCCCTTGTTCCAGGATGGGA	10
71	CTCCTCCTTCTACACGCTATCATTTAGTGGTTAGTAGAGATCAGACAAACGATCGCAGCGATGACAAACC	20
141	TGCAAGATCAAAACCCAAACAGATTGTTCCGTTTCATACGGAGCCTTCTGATGCCAAACACGGACGGCGTC	30
211	CATTCGGACGACACCCCTGGAGAACACACTCTCAGGTCAGAGACCTCGACCTACAATTIGACTGTGGGG	40
281	GACACAGGTCAGGGCTAATTGTCITTTCCCTGGATTCCCTGGCTCAATTGTTGGTGCCTACCTACACAC	50
351	TGCAGGGCAATGGGAACCTACAAGTTTCGATCAGATGCTCCTGACTGCCCCAGAACCTACCGGCCAGTTACAA	60
421	CTACTGCAGGCTAGTGAGTCGGAGTCTCACAGTGAGGTCAAGCACACTTCTGGTGGCGTTTATGCACCTA	70
491	AACGGCACCATAAACGCCGTGACCTTCCAAGGAAGCCTGAGTGAACCTGACAGATGTTAGCTACAATGGGT	
561	TGATGTCTGCAACAGCCCAACATCAACGACAAAATTGGGAACGTCTAGTAGGGGAAGGGGTACCGTCCT	
631	CAGCTTACCCACATCATATGATCTTTGGGTATGTGAGGCTTGGTGACCCCATTTCCCGCAATAGGGCTTGAC	
701	CCAAAAATGGTAGCCACATGTGACAGCAGTGACAGGCCCCAGAGTCTACACCATAACTGCAGCCGATGATT	
771	ACCAATTCTCATCACAGTACCAACCAAGGTGGGTAAACAATCACACTGTTCTCAGCCAACTTGATGCCAT	
841	CACAAGCCTCAGCGTTGGGGAGAGCTCGTGTTCAAACAAGCGTCCACGGCTTGACTGGCGCCACCC	
911	ATCTACCTCATAGGCTTTGATGGGACAAACGGTAATCACCAAGGCTGTGGCCGCAACAATGGGCTGACGA	
981	CCGSCACCGACAACCTTATGCCATTCAATCTTGTGATTCCAACAACGAGATAACCCAGCCAATCACATC	
1051	CATCAAACTGGAGATAGTGACCTCCAAAAGTGGTGGTTCAGGCAGGGGATCAGATGTCATGGTCGGCAAGA	
1121	GGGAGCCTAGCAGTGACGATCCATGGTGGCAACTATCCAGGGGCCCTCCGTCCCGTCACGCTAGTGGCCT	
1191	ACGAAAGAGTGGCAACAGGATCCGTCGTTACGGTCGCTGGGGTGAGCAACTTCGAGCTGATCCCAAAATCC	
1261	TGAACTAGCAAAGAACCCTGGTTACAGAAACGGCCGATTTGACCCAGGAGCCATGAACCTACACAAAATTG	
1331	ATACTGAGTGAGAGGGACCGTCTTGGCATCAAGACCGTCTGGCCCAACAAGGGAGTACACTGACTTTCGTG	
1401	AATACTTCATGGAGGTGGCCGACCTCAACTCTCCCTGAAGATTGCAGGAGCATTCGGCTTCAAAGACAT	
1471	AATCCGGGCCATAAGGAGGATAGCTGTGCCGTGGTCTCCACATTGTTCCACCTGCCGCTCCCTAGCC	
1541	CATGCAATTGGGGAAGGTGTAGACTACCTGCTGGGCGATGAGGCACAGGCTGCTTCAGGAACTGCTCGAG	
1611	CCGCGTCAGGAAAGCAAGAGCTGCCTCAGGCCGCAATAAGGCAGCTGACTCTCGCCGCCGACAAAGGGTA	
1681	CGAGGTAGTCGGGAATCTATTCAGGTGCCCCAGAAATCCCGTAGTCGACGGGATTCTTGCTTCACCTGGG	
1751	GTAATCCGGGGTGCACACAACCTCGACTCGGTGTTAAGAGAGGGGTGCCACGCTATTCCTGTGGTTATTA	

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1821 CGACAGTGAAGACGCCATGACACCCAAAGCATTGAACAGCAAAAATGTTGCTGTCAATTGAAGGCGTGCG
1891 AGAAGACCTCCAACCTCCATCTCAAAGAGGATCCTTTCATACGAACCTCCTCTGGACACAGAGTCTATGGA
1961 TATGCTCCAGATGGGTACTTCCACTGGAGACTGGAGAGACTACACCGTTGTCCCAATAGATGATGTCT
2031 GGGACGACAGCATTATGCTGTCCAAAGATCCCATACCTCCTATTGTGGAAACAGTGGAATCTAGCCAT
2101 AGCTTACATGGATGTGTTTCGACCCAAAGTCCCAATCCATGTGGCTATGACGGGAGCCCTCAATGCTTGT
2171 GCGAGATTGAGAAAGTAAGCTTTAGAAGCACCAAGCTGCCACTGCACACCGACTTGCCCTTAGGTTGG
2241 CTGGTCCCGGAGCATTTCGATGTAAACACCGGCCCAACTGGCAACGTTTCATCAAACGTTTCCCTCACAA
2311 TCCACGCCACTGGGACAGGCTCCCCTACCTCAACCTACCATACCTTCCACCCCAATGCAGGACGCCAGTAC
2381 CACCTTGCCATGGCTGCATCAGAGTTCAAAGAGACCCCGAAGTACGGGACAGCAGGCTACGGAGTGGAGCTCGG
2451 CAGCAGCCAAACGTGGACCCACTATTCCAATCTGCACCTCAGTGTGTTTCATGTGGCTGGAAGAGAAATGGGAT
2521 TGTGACTGACATGGCCAACTTCGCACCTCAGCGACCCGAACGCCCATCGGATGCGAAATTTTCTTGCAAAC
2591 GCACCACAAGCAGGCAGCAAGTCGAAAGGGCCAAAGTACGGGACAGCAGGCTACGGAGTGGAGGCTCGGG
2661 GCCCACACAGAGGAGACAGAGGGAAGAAAGACACACCGGATCTCAAAGAAGATGGAGACCATGGGCGAT
2731 CTACTTTGCAACACCCAGAAATGGGTAGCACTCAATGGGCACCGAGGCCAAGCCCGCCAGCTAAAGTAC
2801 TGGCAGAACACACGAGAAATACCGGACCCCAACGAGGACTATCTAGACTACGTGCTATGCAGAGAAAGAGCC
2871 GGTGGCATCAGAAGAACAAATCCTAAGGGCAGCTACGTCGATCTACGGGGCTCCAGGACAGGCAGAGCC
2941 ACCCCAAGCTTTCATAGACGAAGTTGCCAAAGTCTATGAAATCAACCATGGACGTTGGCCCAACCAAGAA
3011 CAGATGAAAGATCTGCTCTTGACTGCGATGGAGATGAAGCATCGCAATCCCAGGGCGGCTCTACCAAAGC
3081 CCAAGCCAAACCCAAATGCTCCAACACAGAGACCCCTGGTCGGCTGGCCGCTGGATCAGGACCGTCTC
3151 TGATGAGGACCTTGAGTGAGGCTCCTGGGAGTCTCCCGACACCAACCGGCGAGGTGTGGACACCAATTGG
3221 GCCTTACAACATCCCAAAATTGGATCCGTTTCGCGGGTCCCCCT

Total number of bases 1s: 3261.

DNA sequence composition: 873 A; 909 C; 847 G; 632 T; 0 OTHER;

Sequence name: D78F (SEQ ID NOS: 27 and 29)

Fig.5B

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Fig.6A

1	GGATACGATGGGCTGACCCCTCTGGGAGTCACGAATTAACGTGGCTACTAGGGGCGGATACCCGCCGCTGG	70
71	CCGCCACGTTAGTGGCTCCTCTTCTTGATGATCTGCCACCATTGAGTGACATTTTCAACAGTCCACAGGC	60
141	GCGAAGCACGATCTCAGCAGCGTTCGGCATAAAGCCTACTGCTGGACAAGACGTGGAAAGAACTCTTGATC	50
211	CCTAAAGTTTGGGTGCCACCTGAGGATCCGCTTGCCAGCCCTAGTCGACTGGCAAGTTCCCTCAGAGAGA	40
281	ACGGCTACAAAGTTTTCAGGCCACGGTCTCTGCCCGAGAAATGAGGAGTATGAGACCGACCCAAATACTCCC	30
351	AGACTTAGCATGGATGCGACAGATAGAGGGGCTGTTTTAAACCCACTCTATCTCTCCCTATTGGAGAT	20
421	CAGGAGTACTTCCCAAAGTACTACCCAAACACATCGCCCTAGCAAGGAGAAGCCCAATGCGTACCCGCCAG	10
491	ACATCGCACTACTCAAGCAGATGATTTACCTGTTTCTCCAGGTTCCAGAGGCCAACGAGGCTTAAAGGA	
561	TGAAGTAACCTCTTGACCCAAACATAAGGGACAAGGCTATGGAAGTGGGACCTACATGGGACAAGCA	
631	AATCGACTTGTGGCCATGAAGGAGGTGCCACTGGAAGAAACCCAAACAAGGATCCTCTAAAGCTTGGGT	
701	ACACTTTTGAGAGCATCGCGCAGCTACTTGACATCACACTACCGGTAGGCCACCCGGTGAGGATGACAA	
771	GCCCTGGG TGCCACTCACAAGAGTGCCGTACGGATGTTGGTGCTGACGGGAGACGTAGATGGGACTTT	
841	GAGGTGAAGATTACCTTCCCAAATCAACCTCAAGTCATCAAGTGGACTACCATATGTAGGTGCGACCA	
911	AAGGAGAGACAAATTGGCGAGATGATAGCTATCTCAACCCAGTTTCTCAGAGAGCTATCAACACTGTTGAA	
981	GCAAGGTG CAGGGACAAAGGGTCAACAAGAAGAGCTACTCAGCATGTTAAGTGACTATTGGTACTTA	
1051	TCAT GCGGGCTTTTGTTCCAAAGGCTGAAGGTACGACAAAGTACATGGCTCACCAAGACCCGGAACA	
1121	TATGGTCAGCTCCATCCCCAACACACCTCATGATCTCTATGATCACCTGGCCCGTGATGTCCAAACAGCCC	
1191	AAATAACGTGTTGAACATTGAAGGGTGTCCTCACTCTACAAATTCAACCCGTTTCAAGAGGGTTGAAC	
1261	AGGATCGTCGAGTGGATATTGGCCCGGAAGAACCCAAAGGCTCTTGATATGCGGACAACATATACATTG	
1331	TCCACTCAAACACGTGGTACTCAATTGACCTAGAGAAGGTGAGGCAAACTGCACCTGCCAACACATGCA	
1401	AGCCGCAATGTACTACATACTCACCAGAGGGTGGTCAGACAACGGGACCCCAATGTTCAATCAACACATGG	
1471	GCCACCTTTGCCATGAACATTGCCCTTGCTCTAGTGGTGGACTCATCGTGCCTGATAATGAACCTGCAAA	
1541	TTAAGACCTATGGTCAAGGCAGCGGGAATGCAGCCACGTTTCATCAACAACCACTCTTTGAGCACACTAGT	
1611	GCTTGACCAGTGGAACCTGATGAGACAGCCCCAGACCAGACAGCGAGGAGTTCAAATCAATTGAGGACAAG	
1681	CTAGGTATCAACTTTAAGATTGAGAGGTCCTATGATGATATCAGGGGCAAGCTGAGACAGCTTGTCTCC	
1751	TTGCACAACCAAGGGTACCTGAGTGGGGGGTTGAACCAGAACAAATCCAGGCCCACTGTTGAGCTTGACCT	

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1821 ACTAGGGTGGTCAGCTACATACAGCAAAGATCTCGGGATCTATGTGCCGGTGCTTGACAAGGAACGCCTA
1891 TTTTGTCTGCTGCGTATCCCAAGGGAGTAGAGAACAAAGAGTCTCAAGTCCAAAGTCGGATCGAGCAGG
1961 CATACAAGGTAGTCAGGTATGAGGCGTTGAGTTGGTAGGTGGTTGGAACCTACCCACTCCTGAACAAAGC
2031 CTGCAAGAAATAACGAGGCGCGCTCGGCGGCATCTGGAGGCCAAGGGTTCCCACTCGACGAGTTCCTA
2101 GCCGAGTGGTCTGAGCTGTCAGAGTTCGGTGAGGCCTCGAAGGCTTCAATATCAAGCTGACCGTAACAT
2171 CTGAGAGCCTAGCCGAACCTGAACAAGCCAGTACCCCCAAGCCCCCAATGTCAACAGACCAGTCAACAC
2241 TGGGGACTCAAGGCAGTCAGCAACGCCCTCAAGACCGGTCGGTACAGGAACGAAGCCGGACTGAGTGGT
2311 CTCGTCTTCTAGCCACAGCAAGAAGCCGTCTGCAAGATGCAGTTAAGGCCAAGGCAGAGCCCGAGAAAC
2381 TCCACAAGTCCAAGCCAGACGACCCCGATGCAGACTGGTTCGAAAGATCAGAAACTCTGT CAGACCTTCT
2451 GGAGAAAGCCGACATCGCCAGCAAGGTGCCCACTCAGCACTCGTGGAAACAAGCGACGCCCTTGAAAGCA
2521 GTTCAGTCGACTTCGGTGTACACCCCCAAGTACCCAGAAGTCAAGAACCCACAGACCGCTCCAACCCCG
2591 TTGTTGGGCTCCACCTGCCCGCCAAGAGAGCCACCGGTGTCCAGGCCGCTCTTCTCGGAGCAGGAACGAG
2661 CAGACCAATGGGGATGGAGGCCCCAACACGGTCCAAGAACGCCGTGAAAATGGCCAAACGGCGGCAACGC
2731 CAAAAGGAGAGCCGCTAACAGCCATGATGGGAACCACTCAAGAGAGGACACTAATCCCAGACCCCGTAT
2801 CCCCAGGCTTCGCCCTGCGGGGGCCCCC

Total number of bases is: 2827.

DNA sequence composition: 796 A; 770 C; 724 G; 537 T; 0 OTHER;

Sequence name: P2B (SEQ ID No: 25)

Fig.6B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12955**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/184.1, 204.1, 816, 826; 435/71.1, 235.1, 236, 237, 238, 239, 320.1; 536/23.72

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN-MEDLINE, BIOSIS, CAPLUS, CABA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUNDT et al. Complete Nucleotide Sequences of 5'- and 3' Noncoding Regions of Both Genome Segments of Different Strains of Infectious Bursal Disease Virus. Virology. 1995, Vol. 209, pages 10-18, see entire document.	1-2, 4-20
X	US 4,530,831 A (LUTTICKEN ET AL) 23 JULY 1985 (07/23/85), see entire document.	7, 15-20
X	US 5,192,539 A (VAN DER MAREL ET AL) 09 MARCH 1993 (09/03/93), see entire document.	1-3, 7, 15-20
X	MUNDT et al. Identification of a novel viral protein in infectious bursal disease virus-infected cells. Journal of General Virology. 1995, Vol. 76, pages 437-443, see entire document.	8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 SEPTEMBER 1997

Date of mailing of the international search report

10 NOV 1997

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12955

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAYLISS et al. A comparison of the sequences of segment A of four infectious bursal disease virus strain and identification of a variable region in VP2. Journal of General Virology. 1990, Vol. 71, pages 1303-1312, see entire document.	1-2, 5-8, 10-13
Y	MORGAN et al. Sequence of the Small Double-Stranded RNA Genomic Segment of Infectious Bursal Disease Virus and Its Deduced 90kDa Product. Virology. 1988, Vol. 163, pages 240-242, see entire document.	1-20
Y	SPIES et al. Nucleotide sequence of infectious bursal disease virus genome segment A delineates two major open reading frames. Nucleic Acids Research. 1989, Vol. 17, No. 19, page 7982, see entire document.	1-20
Y	WO 91/16925 A1 (UNIVERSITY OF MARYLAND at COLLEGE PARK) 14 NOVEMBER 1991 (14/11/91), see entire document.	1-20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/12955

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 39/00, 39/38, 39/12; C12P 21/04; C12N 7/00, 7/01, 7/02, 7/04, 7/06, 7/08, 15/00, 15/09, 15/63, 15/70, 15/74

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

424/184.1, 204.1, 816, 826; 435/71.1, 235.1, 236, 237, 238, 239, 320.1; 536/23.72